

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ :		A1	(11) International Publication Number: WO 00/58305 (43) International Publication Date: 5 October 2000 (05.10.00)
C07D 401/12, 401/06, 211/14, 211/22, A61K 31/445, A61P 11/00, 19/00, 31/00			
(21) International Application Number: PCT/SE00/00563			& D Charnwood, Bakewell Road, Loughborough, Leisc. LE11 5RH (GB). THOM, Stephen [GB/GB]; AstraZeneca,
(22) International Filing Date: 22 March 2000 (22.03.00)			R & D Charnwood, Bakewell Road, Loughborough, Leisc. LE11 5RH (GB).
(30) Priority Data: 9901117-3 26 March 1999 (26.03.99) SE 9902194-1 10 June 1999 (10.06.99) SE			(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).
(71) Applicant (for all designated States except MG US): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).			(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(71) Applicant (for MG only): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).			
(72) Inventors; and			Published
(75) Inventors/Applicants (for US only): BAXTER, Andrew [GB/GB]; AstraZeneca, R & D Charnwood, Bakewell Road, Loughborough, Leisc. LE11 5RH (GB). BROUGH, Stephen [GB/GB]; AstraZeneca, R & D Charnwood, Bakewell Road, Loughborough, Leisc. LE11 5RH (GB). KINDON, Nicholas [GB/GB]; AstraZeneca, R & D Charn- wood, Bakewell Road, Loughborough, Leisc. LE11 5RH (GB). MCINALLY, Thomas [GB/GB]; AstraZeneca, R & D Charnwood, Bakewell Road, Loughborough, Leisc. LE11 5RH (GB). ROBERTS, Bryan [GB/GB]; AstraZeneca, R			With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: NOVEL COMPOUNDS			
$\begin{array}{c} \text{R}^1 - (\text{Q})_m - \text{T} - (\text{CR}^2\text{R}^3)_n - \text{V} \\ \text{R}^4 \end{array} \quad (I)$			
(57) Abstract			
<p>The invention provides compounds of general formula (I) wherein: R¹ represents optionally substituted C₁-C₁₂ alkyl or optionally substituted 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur; m is 0-1; Q represents OCH₂, C₁-C₄ alkylene or C₂-C₄ alkenylene; T represents C(O)NH, or when m is 0, T may additionally represent a bond or NH, or when m is 1 and Q represents C₁-C₄ alkylene, T may additionally represent NH; n is 1-4; each R² and R³ independently represents H or C₁-C₄ alkyl; V represents N, and W represents N or CH; X represents O, C(O), CH(OH), SO₂, NH or N(C₁-C₆ alkyl), provided that when W represents N, then X represents either C(O) or SO₂ and when W represents CH, then X is other than SO₂; R⁴ represents optionally substituted phenyl; R⁵ and R⁶ each independently represent H, C₁-C₆ alkyl or hydroxyC₁-C₆ alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring; R⁷ and R⁸ each independently represent H or C₁-C₆ alkyl; and R⁹ represents OH or -NR⁷R⁸; processes for their preparation, pharmaceutical compositions containing them and their use in therapy.</p>			

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NOVEL COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

5

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved 10 four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

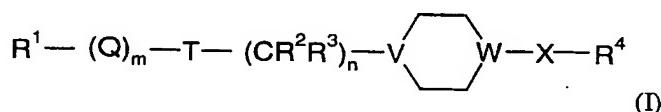
15 The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and 20 MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, 25 CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Certain piperidinyl derivatives and piperazinyl derivatives are known from U.S. Patents Nos. 3 787 419, 4 559 349 and 5 210 086 for use respectively as central nervous system depressants, antipsychotic agents and as α_1 -adrenoreceptor antagonists.

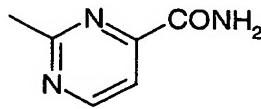
- 5 In accordance with the present invention, there is therefore provided a compound of general formula



wherein:

- 10 R^1 represents a C_1 - C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio and C_1 - C_6 alkoxy carbonyl groups, or
 R^1 represents a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one or more substituents independently selected from halogen atoms, and cyano, nitro, hydroxyl, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy carbonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-NR^5R^6$, C_3 - C_6 cycloalkylamino, C_1 - C_6 alkylthio, C_1 - C_6 alkylthio C_1 - C_6 alkyl, C_1 - C_6 alkyl carbonylamino, $-C(O)NR^7R^8$, sulphonamido ($-SO_2NH_2$), (di) C_1 - C_6 alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and $C(O)R^9$ -substituted C_1 - C_6 alkyl or C_1 - C_6 alkoxy groups;
- 15 m is 0 or 1;
- 20 Q represents a group OCH_2 , C_1 - C_4 alkylene or C_2 - C_4 alkenylene;
 T represents a group $C(O)NH$, or when m is 0, T may additionally represent a bond or a group NH , or when m is 1 and Q represents C_1 - C_4 alkylene, T may additionally represent a group NH ;

- n is 1, 2, 3 or 4;
- each R² independently represents a hydrogen atom or a C₁-C₄ alkyl group;
- each R³ independently represents a hydrogen atom or a C₁-C₄ alkyl group;
- V represents a nitrogen atom;
- 5 W represents a nitrogen atom or a group CH;
- X represents an oxygen atom or a group C(O), CH(OH), NH or N(C₁-C₆ alkyl), provided that when W represents a nitrogen atom, then X represents C(O);
- R⁴ represents a phenyl group optionally substituted by one or more substituents independently selected from halogen atoms, and amino, nitro, cyano, sulphonyl (-SO₃H),
- 10 sulphonamido (-SO₂NH₂), C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy and C₁-C₆ alkylsulphonyl groups;
- R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₆ alkyl or hydroxyC₁-C₆ alkyl group, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring;
- 15 R⁷ and R⁸ each independently represent a hydrogen atom or a C₁-C₆ alkyl group; and R⁹ represents a hydroxyl or -NR⁷R⁸ group;
- with the provisos that
- (a) when m is 0, T is CONH, n is 2, 3 or 4 and each R² and R³ represents hydrogen, W is CH, X is C(O) or CH(OH) and R¹ represents a substituted 3- to 10-membered unsaturated
- 20 ring system, then the one or more substituents in the ring system do not include hydroxyl, halogen, C₁-C₆ alkoxy or C₁-C₆ haloalkoxy, and
- (b) when W is N, X is C(O), R⁴ represents 3-trifluoromethylphenyl, m is 0 and T is a bond, then R¹ and (CR²R³)_n taken together do not represent a C₁-C₆ alkyl group, and
- (c) when W is CH, X is O, n is 2 or 3 and each R² and R³ represents hydrogen, m is 0 and
- 25 T is NH, then R¹ does not represent a group



; or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Further, the alkyl moieties in a dialkylamino, di(hydroxyalkyl)amino or dialkylsulphonamido substituent group may be the same or
5 different.

R¹ represents a C₁-C₁₂, preferably C₁-C₁₀, alkyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from cyano, hydroxyl, C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy,
10 pentoxy or hexoxy), C₁-C₆, preferably C₁-C₄, alkylthio (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylthio) and C₁-C₆, preferably C₁-C₄, alkoxy carbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxy carbonyl) groups, or
R¹ represents a 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms
15 independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen atoms (fluorine, chlorine, bromine or iodine), and cyano, nitro, hydroxyl, C₁-C₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl or hexyl), C₃-C₆ cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl),
20 C₁-C₆ alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy), C₁-C₆ alkoxy carbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-, pentoxy- or hexoxy carbonyl), C₁-C₆ haloalkyl (e.g. trifluoromethyl), C₁-C₆ haloalkoxy (e.g. trifluoromethoxy), -NR⁵R⁶, C₃-C₆ cycloalkylamino (cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexylamino), C₁-C₆ alkylthio (e.g. methyl-, ethyl-, propyl-, butyl-,
25 pentyl- or hexylthio), C₁-C₆ alkylthioC₁-C₆ alkyl (e.g. methylthiomethyl), C₁-C₆ alkylcarbonylamino (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylcarbonylamino), -C(O)NR⁷R⁸, sulphonamido (-SO₂NH₂),
(di)C₁-C₆ alkylsulphonamido (e.g. (di)methylsulphonamido or (di)ethylsulphonamido), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl,

furanyl, and C(O)R⁹-substituted C₁-C₆ alkyl or C₁-C₆ alkoxy groups, the alkyl and alkoxy moieties being as defined above.

The 3- to 10-membered saturated or unsaturated ring system in the group R¹ may be 5 monocyclic, or polycyclic comprising 2 or more fused rings, examples of which include cyclobutyl, cyclopentyl, cyclohexyl, norbornenyl, adamantyl, piperidyl, phenyl, naphthyl, naphthyridinyl, 1,3-benzodioxolyl, pyrazolyl, furanyl, pyridyl, thienyl, benzoxazolyl, benzothiazolyl, chromonyl, imidazolyl, quinolinyl, isoquinolinyl, benzimidazolyl, pyrimidinyl, pyrazolopyrimidinyl, thienopyrimidinyl, 10 thiazolopyrimidinyl, pyrimidinedione, pyrazinyl, pyridazinyl, purinyl, quinoxalinyl, thiazolyl, isothiazolyl and 2,4-dioxo-3,4-dihydro-quinazolinyl.

Preferably, R¹ represents a C₁-C₁₀ alkyl group optionally substituted by one or two 15 substituents independently selected from cyano, hydroxyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio and C₁-C₄ alkoxy carbonyl groups, or

R¹ represents a 3- to 10-membered saturated or unsaturated ring system comprising up to 20 two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one, two or three substituents independently selected from halogen atoms, and cyano, nitro, hydroxyl, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, C₁-C₃ haloalkyl, C₁-C₃ haloalkoxy, -NR⁵R⁶, 25 C₃-C₆ cycloalkylamino, C₁-C₄ alkylthio, C₁-C₄ alkylthioC₁-C₄ alkyl, C₁-C₄ alkylcarbonylamino, -C(O)NR⁷R⁸, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and C(O)R⁹-substituted C₁-C₄ alkyl or C₁-C₄ alkoxy groups.

Preferably Q represents a group OCH₂, C₁-C₃ alkylene or C₂-C₃ alkenylene.

Each R² independently represents a hydrogen atom or a C₁-C₄ alkyl (e.g. methyl, ethyl, 30 propyl, isopropyl or butyl) group, and is especially a hydrogen atom.

Each R³ independently represents a hydrogen atom or a C₁-C₄ alkyl (e.g. methyl, ethyl, propyl, isopropyl or butyl) group, and is especially a hydrogen atom.

5 Preferably n is 2 or 3.

X preferably represents an oxygen atom or a group C(O) or NH.

R⁴ represents a phenyl group optionally substituted by one or more (e.g. one, two, three or
10 four) substituents independently selected from halogen atoms (fluorine, chlorine, bromine or iodine), and amino, nitro, cyano, sulphonyl (-SO₃H), sulphonamido (-SO₂NH₂), C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl), C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl), C₁-C₆, preferably C₁-C₄, haloalkoxy (e.g. trifluoromethoxy) and C₁-C₆, preferably C₁-C₄, alkylsulphonyl (e.g. methyl-, ethyl-,
15 propyl-, butyl-, pentyl- or hexylsulphonyl) groups.

Preferably, R⁴ represents a phenyl group optionally substituted by one or two halogen atoms, particularly chlorine atoms.

20 R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₆, preferably C₁-C₄, alkyl or hydroxyC₁-C₆, preferably C₁-C₄, alkyl group, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring. The alkyl moiety in each case may, for example, be a methyl, ethyl, propyl, butyl, pentyl or hexyl group. In the hydroxyalkyl group, the hydroxyl group may be attached to
25 any suitable carbon atom of the alkyl moiety.

R⁷ and R⁸ each independently represent a hydrogen atom or a C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) group. Preferably, R⁷ and R⁸ each independently represent a hydrogen atom or a methyl group.

R^9 represents a hydroxyl or, preferably, $-NR^5R^6$ group.

Examples of particularly preferred compounds of the invention include:

- 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide,
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-ethoxybenzamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-isopropoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-ethoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide
10 hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethoxy)benzamide
hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide hydrochloride,
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride,
3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide hydrochloride,
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide hydrochloride,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride,
2-[3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl]-N,N-dimethylacetamide hydrochloride,
25 N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride,
3,4-Dichloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}benzamide,
4-Chloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide hydrochloride,
N~7~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methyl[1,3]thiazolo[4,5-
30 d]pyrimidine-2,7-diamine,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-9-methyl-9H-purin-6-amine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzothiazol-2-amine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzoxazol-2-amine,
6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrazinamine,
5 6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-pyridazinamine,
6-{(2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl)amino}-1,3-dimethyl-2,4(1H,3H)-
pyrimidinedione,
N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-
benzamide, hydrochloride salt,
10 N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-methoxy-
benzamide, hydrochloride salt,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-(3-methoxybenzyl)amine
dihydrochloride,
15 3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-
quinazolinedione,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-nitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methylbenzamide,
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-dinitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-iodobenzamide,
4-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
4-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
30 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methylbenzamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-nitrobenzamide,
3-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
3,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,
5 2,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methylbenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-iodobenzamide,
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-nitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,
10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-5-(trifluoromethyl)benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide,
3,5-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)benzamide,
15 3-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
2-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,
3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
2-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-difluorobenzamide,
2,3-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-naphthamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-6-(trifluoromethyl)benzamide,
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-difluorobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,
Methyl 4-({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)-4-oxobutanoate,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclobutanecarboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxyacetamide,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclohexanecarboxamide,
- (E)-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,
- 2-Chloro-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}nicotinamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclopentanecarboxamide,
- 10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenoxyacetamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,
- 4-(tert-Butyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methylbenzamide,
- 15 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-nitrobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methylbenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-cyanobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-furamide,
- 20 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-nitrobenzamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-naphthamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1,3-thiazole-4-carboxamide,
- 25 N~2~-Cyclopropyl-N~4~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine,
- 2-[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl]amino)-1-ethanol,
- 2-[[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-
- 30 pyrimidinyl](methyl)amino]-1-ethanol,

- N~4~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~~phenyl-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)-4-pyrimidinamine,
- N~4~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2,4-pyrimidinediamine,
- 5 N~4~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,
- 2-Chloro-N~4~~cyclopropyl-N~6~~{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenyl-2-pyrimidinamine,
- 10 N~2~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(propylsulfanyl)-2-pyrimidinamine,
- 15 N~2~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~~phenyl-2,4-pyrimidinediamine,
- N~4~~Cyclopropyl-N~2~~{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}[1,8]naphthyridin-2-amine,
- 20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-pyridinyl)-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-dimethoxy-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-furyl)-2-pyrimidinamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1-methyl-1H-pyrazolo[3,4-
- 25 d]pyrimidin-4-amine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-purin-6-amine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methylthieno[3,2-d]pyrimidin-4-amine,
- 30

- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}cyclohexanecarboxamide,
5 (E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-phenoxyacetamide,
(E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(4-nitrophenyl)-2-propenamide,
2-(1-Adamantyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}acetamide,
(4-Chlorophenyl)(1-{2-[(2-fluoro-4,5-dimethoxybenzyl)amino]ethyl}-4-
10 piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(3,4,5-trimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(3-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl){1-[2-(isobutylamino)ethyl]-4-piperidinyl)methanone,
4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-ethylhexanenitrile,
15 (4-Chlorophenyl)(1-{2-[(7-hydroxy-3,7-dimethyloctyl)amino]ethyl}-4-
piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-{[(6-nitro-1,3-benzodioxol-5-yl)methyl]amino}ethyl)-4-
piperidinyl)methanone,
[1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-
20 chlorophenyl)methanone,
(4-Chlorophenyl)[1-(2-{[3-nitro-4-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-
piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-{[(E)-3-(4-nitrophenyl)-2-propenyl]amino}ethyl)-4-
piperidinyl)methanone,
25 (4-Chlorophenyl){1-[2-((5-(3-nitrophenyl)-2-furylmethyl)amino)ethyl]-4-
piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-{[5-nitro-2-(2-pyridinylsulfanyl)benzyl]amino}ethyl)-4-
piperidinyl)methanone,
6-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-2-
30 (methylsulfanyl)nicotinonitrile,

- {1-[2-({[5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)ethyl]-4-piperidinyl}(4-chlorophenyl)methanone,
(4-Chlorophenyl)[1-(2-{[3-(methylsulfanyl)butyl]amino}ethyl)-4-piperidinyl]methanone,
(4-Chlorophenyl)[1-(2-{[(4-phenyl-4-piperidinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
5 (4-Chlorophenyl)[1-(2-{[(1-phenyl-1H-pyrazol-5-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,
Ethyl 3-[{(2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}-amino)methyl]cyclohexanecarboxylate,
10 N-{4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]phenyl}acetamide,
(4-Chlorophenyl)(1-{2-[(2,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(2,6-dichlorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(2-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
15 (4-Chlorophenyl)[1-(2-{[(3-methyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-methoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,
3-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4H-chromen-4-one,
20 [1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,
(4-Chlorophenyl)[1-(2-{[(2,6-dichloro-4-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
(4-Chlorophenyl)[1-(2-{[(2-phenyl-1H-imidazol-4-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,
25 (4-Chlorophenyl)[1-(2-{[(5-ethyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
(4-Chlorophenyl)[1-(2-{[(2-chloro-3-quinoliny) methyl]amino}ethyl)-4-piperidinyl]methanone,
(4-Chlorophenyl)[1-(2-{[(6-methyl-2-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
30 (4-Chlorophenyl)[1-(2-{[(6-methyl-2-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,

- (4-Chlorophenyl)(1-{2-[{(3-quinolinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
4-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-1,5-dimethyl-2-phenyl-
1,2-dihydro-3H-pyrazol-3-one,
(4-Chlorophenyl)(1-{2-[{(4-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
5 (4-Chlorophenyl)(1-{2-[{(3-hydroxy-4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[{(3,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(1-{2-[{(2-Chloro-6-fluorobenzyl)amino]ethyl}-4-piperidinyl)(4-chlorophenyl)methanone,
[1-(2-{[(4-Bromo-1H-pyrazol-3-yl)methyl]amino}ethyl)-4-piperidinyl](4-
chlorophenyl)methanone,
10 3-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-6,7-dimethyl-4H-
chromen-4-one,
2-{2-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-4-nitrophenoxy}acetic
acid,
(4-Chlorophenyl)[1-(2-{[(1-methyl-1H-benzimidazol-2-yl)methyl]amino}ethyl)-4-
15 piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-{[(2,4-dimethoxy-5-pyrimidinyl)methyl]amino}ethyl)-4-
piperidinyl)methanone,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylamino)benzamide,
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-4-methylbenzamide,
3-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzodioxole-5-carboxamide,
4-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluoro-4-methoxybenzamide,
25 5-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methyl-2-furamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,5-dimethyl-2-furamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-ethoxy-1-benzofuran-2-
carboxamide,

- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-5-methoxy-1-benzofuran-2-carboxamide,
- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-7-methoxy-1-benzofuran-2-carboxamide,
- 5 N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-fluorophenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(2-methoxyphenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3-methylphenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(2-methylphenyl)acetamide, 2-(3-Bromophenyl)-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]acetamide,
- 10 2-(2-Chlorophenyl)-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]acetamide, 2-(4-Chlorophenyl)-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-[2-(trifluoromethyl)phenyl]acetamide,
- 15 2-(3-Chlorophenyl)-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3,4-dimethoxyphenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-methoxyphenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3,4-dichlorophenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3-fluoro-4-methoxyphenyl)acetamide,
- 20 N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-ethoxyphenyl)acetamide, 2-(1,3-Benzodioxol-5-yl)-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-[4-(dimethylamino)phenyl]acetamide,
- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-methylphenyl)acetamide,
- 25 N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3,4-difluorophenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3-methoxyphenyl)acetamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-phenylbutanamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-phenylpropanamide, N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-(3-methoxyphenyl)propanamide,
- 30 2-Amino-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-1,3-thiazole-4-carboxamide,

- 2-(Acetylamino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-pyridinyl)-1,3-thiazole-4-carboxamide,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-dimethyl-1,3-thiazole-5-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,5-dimethyl-1,3-oxazole-4-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-imidazole-4-carboxamide,
- 10 N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide, hydrochloride salt,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2,6-dimethoxy-4-pyrimidinamine,
- 15 N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-6-
- 20 (trifluoromethyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,
- 25 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-methyl-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(ethylsulfanyl)-6-methyl-4-pyrimidinamine,
- N~2~-Cyclopropyl-N~4~-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2,4-
- 30 pyrimidinediamine,

- 2-{{4-((3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl)amino)-2-pyrimidinyl}amino}-1-ethanol,
- 2-{{4-((3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl)amino)-2-pyrimidinyl}(methyl)amino}-1-ethanol,
- 5 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-4-pyrimidinamine,
- N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2,4-pyrimidinediamine,
- N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,
- 10 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-phenyl-2-pyrimidinamine,
- N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-fluoro-2,4-pyrimidinediamine,
- N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine,
- 15 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(trifluoromethyl)-2-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(propylsulfanyl)-2-pyrimidinamine,
- N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~-phenyl-2,4-pyrimidinediamine,
- 20 N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,6-dimethyl-2,4-pyrimidinediamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}[1,8]naphthyridin-2-amine,
- 2-{[2-((3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl)amino)-4-pyrimidinyl]amino}-1-
- 25 ethanol,
- 2-[[2-((3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl)amino)-4-pyrimidinyl](methyl)amino]-1-ethanol,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-pyridinyl)-2-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-thienyl)-2-pyrimidinamine,
- 30 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrimidinamine,

- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4,6-dimethoxy-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-furyl)-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(2-thienyl)-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-purin-6-amine,
5 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-7-methylthieno[3,2-d]pyrimidin-4-amine,
N~7~~{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine,
10 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-9-methyl-9H-purin-6-amine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,
5-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine,
15 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-pyridinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzothiazol-2-amine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzoxazol-2-amine,
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrazinamine,
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-pyridazinamine,
20 6-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,6-dimethoxy-4-pyrimidinamine,
N~4~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,N~2~~dimethyl-2,4-pyrimidinediamine,
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,
30

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-methyl-4-pyrimidinamine, and

N-4--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-N-2--phenyl-2,4-pyrimidinediamine.

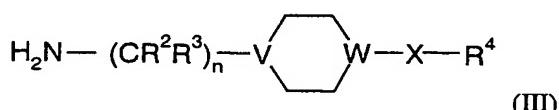
5

The present invention further provides a process for the preparation of a compound of formula (I) which comprises

- (i) when T represents a group $\text{C}(\text{O})\text{NH}$, reacting a compound of general formula



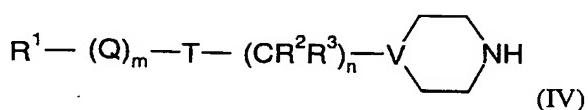
wherein L^1 represents a leaving group (e.g. a hydroxyl or halide, such as chloride, group) and R^1 , m and Q are as defined in formula (I), with a compound of general formula



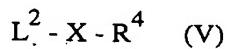
15 or an acid addition salt thereof (e.g. trifluoroacetate) wherein n, R², R³, V, W, X and R⁴
are as defined in formula (I); or

- (ii) when T represents a group $\text{C}(\text{O})\text{NH}$ and W represents a nitrogen atom, reacting a compound of general formula

20



wherein R¹, m, Q, T, n, R², R³ and V are as defined in formula (I), with a compound of general formula



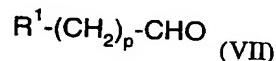
25 wherein L^2 represents a leaving group (e.g. a halogen atom) and X and R^4 are as defined in formula (I); or

(iii) when T represents a group NH and m is 0, reacting a compound of general formula
 R^1-L^3 (VI)

wherein L^3 represents a leaving group (e.g. a halogen atom) and R^1 is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

5

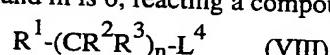
(iv) when T represents a group NH, m is 1 and Q represents C₁-C₄ alkylene, reacting a compound of general formula



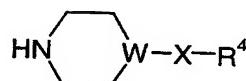
wherein p is 0, 1, 2 or 3 and R^1 is as defined in formula (I), with a compound of formula

10 (III) as defined in (i) above; or

(v) when T represents a bond and m is 0, reacting a compound of general formula



15 wherein L^4 represents a leaving group such as a halogen atom (e.g. chlorine) and n, R^1 , R^2 and R^3 are as defined in formula (I), with a compound of general formula



(IX)

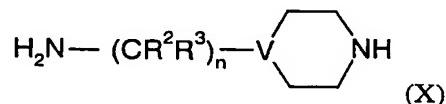
20 wherein W, X and R^4 are as defined in formula (I);

and optionally after (i), (ii), (iii), (iv) or (v) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

25

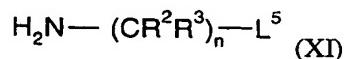
The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as dimethylformamide or dichloromethane at a temperature of, for example, 15°C or above such as a temperature in the range from 20 to 100°C.

Compounds of formula (III) in which W represents a nitrogen atom may be prepared by reacting a compound of general formula



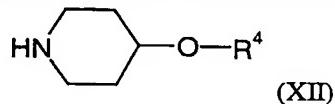
in which n, R², R³ and V are as defined in formula (I) with a compound of formula (V) as defined above.

Compounds of formula (X) can be prepared by reacting piperazine with a compound of general formula



wherein L⁵ represents a halogen atom such as a bromine atom and n, R² and R³ are as defined in formula (I).

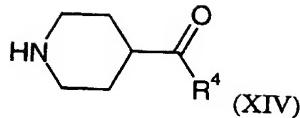
Compounds of formula (III) in which W represents a group CH and X represents an oxygen atom may be prepared by reacting a compound of general formula



in which R⁴ is as defined in formula (I), with a compound of formula (XI).

Compounds of formula (XII) may be prepared by reacting 4-piperidinol with a compound of general formula (XIII), R⁴-OH, wherein R⁴ is as defined in formula (I), in the presence of a coupling agent such as diethyl azodicarboxylate and triphenylphosphine and in a solvent such as benzene or tetrahydrofuran at a temperature typically in the range from 20 to 30 °C.

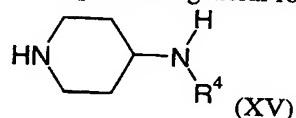
Compounds of formula (III) in which W represents a group CH and X represents a group C(O) may be prepared by reacting a compound of general formula



wherein R⁴ is as defined in formula (I), with a compound of formula (XI).

Compounds of formula (III) in which W represents a group CH and X represents a group CH(OH) may be prepared by reducing/hydrogenating a corresponding compound of formula (III) in which X represents C(O) using techniques known in the art.

Compounds of formula (III) in which W represents a group CH and X represents a group NH may be prepared by reacting a compound of general formula



in which R⁴ is as defined in formula (I), with a compound of formula (XI).

Compounds of formula (XV) may be prepared by reacting 4-piperidone with a compound of general formula (XVI), R⁴-NH₂, wherein R⁴ is as defined in formula (I), in the presence of a reducing agent such as sodium cyanoborohydride or sodium borohydride and in a solvent such as methanol or benzene at a temperature typically in the range from 15 20 to 90 °C.

Compounds of formula (III) in which W represents a group CH and X represents a group N(C₁-C₆ alkyl) may be prepared by alkylating a corresponding compound of formula (III) in which X represents a group NH, using techniques conventional in the art.

Compounds of formula (IV) may be prepared by reacting a compound of formula (II) with a compound of formula (X).

Compounds of formulae II, V, VI, VII, VIII, IX, XI, XIII, XIV and XVI are either commercially available, are well known in the literature or may be prepared easily using known techniques.

- 5 Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example, compounds of formula (I) in which R¹ represents an alkoxy-substituted phenyl group can be converted to compounds of formula (I) in which R¹ represents a hydroxy-substituted phenyl group by reaction with boron tribromide in a solvent such as dichloromethane. Further, compounds of formula (I) in which X represents C(O) can be converted to compounds of formula (I) in which X represents CH(OH) by reaction with triethylsilane and trifluoroacetic acid in a solvent such as dichloromethane.
- 10

- It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

- 20
 - 25
- The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

- The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

- 30
- Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers

of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

- The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR1 and/or CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

10 Examples of these conditions are:

- (1) (**the respiratory tract**) obstructive airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;
- (2) (**bone and joints**) rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;
- (3) (**skin**) psoriasis, atopical dermatitis, contact dermatitis and other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

- (4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;
- 5 (5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; and
- 10 (6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.
- 15 Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

25 The invention also provides a method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

- 5 The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

10 15 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

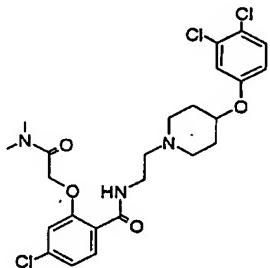
- 15 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

20 25 The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The invention will now be further explained by reference to the following illustrative examples.

Example 1

- 5 **4-Chloro-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-2-[2-(dimethylamino)-2-oxoethoxy]benzamide**



(i) **tert-Butyl 4-(3,4-dichlorophenoxy)-1-piperidinecarboxylate**

- Diethyl azodicarboxylate (12.6ml) was added to a solution of triphenylphosphine (20.8g) in tetrahydrofuran (300ml) at 0° C. After 15 minutes 3,4-dichlorophenol (12.9g) was added, after a further 10 minutes tert-butyl 4-hydroxy-1-piperidinecarboxylate (14.5g) in tetrahydrofuran (100ml) was added dropwise over 0.5 hour. The solution was stirred at room temperature for 5 hours and concentrated to a small volume. The residue was partitioned between ether and brine. The organic phase was separated, dried and evaporated to a gum. Purification by chromatography (ethyl acetate : isohexane 95:5) gave the sub-titled product as an oil (20g).

MS: APCI(+ve): 246 (M-BOC+2H)

20 (ii) **4-(3,4-Dichlorophenoxy)piperidine**

The product from step (i) was dissolved in dichloromethane (200ml) and trifluoroacetic acid (100ml) was added. After 18 hours at room temperature the solution was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (16.2g).

25 (iii) **tert-Butyl 2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethylcarbamate**

The product from step (ii) (6.55g) was dissolved in DMF (50ml) and triethylamine (7.9ml) was added. tert-Butyl 2-bromoethylcarbamate (4.3 g) in DMF (5ml) was added and the solution stirred at room temperature for 3 days. Ethyl acetate and water were added, the organic phase separated, dried and evaporated to a gum. Purification by chromatography (dichloromethane : methanol 95:5) gave the sub-titled product as a gum (5.7g).

MS: APCI(+ve): 389(M+H)

(iv) 2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethylamine trifluoroacetate

- 10 The product from step (iii) was dissolved in dichloromethane (200ml) and trifluoroacetic acid (100ml) added. After 18hrs at room temperature the solvent was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (5.7g).

MS: APCI(+ve): 290(M+H)

15

(v) 2-(Dimethylamino)-2-oxoethyl 4-chloro-2-[2-(dimethylamino)-2-oxoethoxy]benzoate

- A mixture of 4-chloro-2-hydroxybenzoic acid (5g), Cs₂CO₃ (17.5g) and 2-chloro-N,N-dimethylacetamide (6.6g) was stirred and heated at 70 °C for 3 hours. Water and ethyl acetate were added, the organic phase separated, dried and concentrated to a gum which was purified by chromatography (ethyl acetate : methanol, 9:1) to give the sub-titled product as a solid (8.0g).

MS: APCI(+ve) 343(M+H)

- 25 Melting point: 140-141 °C

(vi) 4-Chloro-2-[2-(dimethylamino)-2-oxoethoxy]benzoic acid

The product from step (v) (1.0g) was dissolved in a 2 : 1 water : methanol mixture (15ml) and LiOH.H₂O added. After 2 hours 2M aqueous HCl solution and ethyl acetate were

added, the organic phase separated, dried and concentrated to give the sub-titled product as a solid (1.2g).

MS: APCI(+ve) 258(M+H)

5 Melting point: 141-142 °C

(vii) 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide

The product from step (vi) (0.3g) and N,N-carbonyldiimidazole (0.19g) were dissolved in 10 DMF (20ml) and the solution stirred at room temperature for 1 hour. The product from step (iv) (0.42g) and triethylamine (0.32ml) were added. After 20 hours water and ether were added, the organic phase separated, dried and concentrated to a gum which was purified by chromatography (dichloromethane : methanol, 93:7) to give the titled product as a solid (0.38g).

15

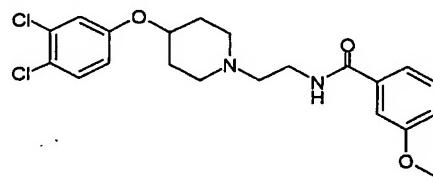
MS: ESI 528.12 (M+H)

¹H NMR: δ(DMSO) 9.17 (t, 1H), 7.88 (d, 1H), 7.48 (d, 1H), 7.38 (d, 1H), 7.24 (d, 1H), 7.13 (dd, 1H), 6.99 (dd, 1H), 5.11 (s, 2H), 4.32 (m, 1H), 3.42 (m, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.73 (m, 2H), 2.50 (m, 2H), 2.30 (m, 2H), 1.90 (m, 2H), 1.59 (m, 2H).

20 Melting point: 139-40 °C

Example 2

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-ethoxybenzamide hydrochloride



25

The product of Example 1 step (iv) (0.4g) was dissolved in DMF (10ml), PyBrop (0.541g), 3-ethoxybenzoic acid (0.167g) and N,N-di-isopropylethylamine (0.5g) were added. After

18 hours at room temperature chloroform and aqueous NaHCO₃ solution were added. The organic phase was separated, dried and concentrated to leave a gum which was purified by chromatography (ethyl acetate : methanol 97:3) to give an oil. Addition of 1.0M ethereal hydrogen chloride solution gave the titled product as a solid (0.14g).

5

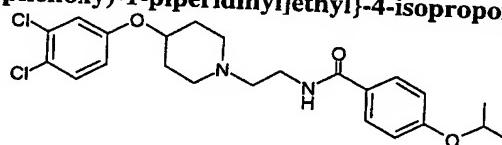
MS: ESI 437.14 (M+H)

¹H NMR: δ(DMSO) 8.87 (bs, 1H), 7.50 (m, 3H), 7.40 (m, 2H), 7.06 (m, 2H), 4.83 / 4.62 (m, 1H), 4.08 (q, 2H), 3.67 (m, 3H), 3.47 (m, 1H), 3.17 (m, 3H), 2.20 (m, 2H), 2.03 (m, 2H), 1.34 (t, 3H)

10 Melting point: 191-193 °C

Example 3

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-isopropoxybenzamide



15 Prepared by the same method as Example 2 using 4-isopropoxybenzoic acid without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.12g).

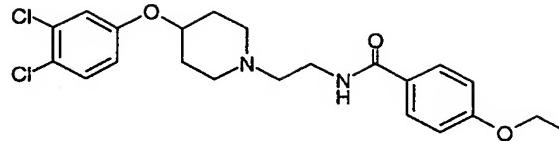
MS: ESI 451.14 (M+H)

20 ¹H NMR: δ(DMSO) 8.22 (t, 1H), 7.8 (m, 2H), 7.49 (d, 1H), 7.25 (d, 1H), 7.00 (m, 3H), 4.7 (m, 1H), 4.45 (m, 1H), 3.36 (m, 2H), 2.73 (m, 2H), 2.48 (m, 2H), 2.29 (m, 2H), 1.91 (m, 2H), 1.60 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H)

Melting point: 113-15 °C

25 Example 4

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-ethoxybenzamide



Prepared by the same method as Example 2 using 4-ethoxybenzoic acid without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.1g).

5

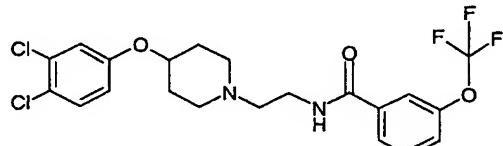
MS: ESI 437.14 (M+H)

¹H NMR: δ(DMSO) 8.22 (t, 1H), 7.79 (d, 2H), 7.49 (d, 1H), 7.25 (d, 1H), 7.00 (m, 3H), 4.5 (m, 1H), 4.07 (q, 2H), 3.37 (q, 2H), 2.73 (m, 2H), 2.47 (m, 2H), 2.30 (m, 2H), 1.91 (m, 2H), 1.60 (m, 2H), 1.34 (t, 3H)

10 Melting point: 118-20 °C

Example 5

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-(trifluoromethoxy)benzamide hydrochloride



15

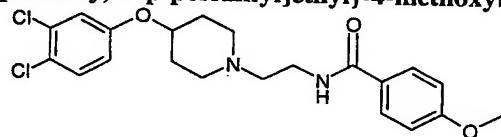
Prepared by the same method as Example 2 using 3-trifluoromethoxybenzoic acid to give the titled product as a solid (0.12g).

MS: ESI 477.09 (M+H)

20 ¹H NMR: δ(DMSO) 10.42 (bs, 1H), 9.11 (bm, 1H), 8.0 (d, 1H), 7.88 (s, 1H), 7.6 (m, 3H), 7.37 (m, 1H), 7.06 (m, 1H), 4.70 (m, 1H), 3.71 (m, 3H), 3.48 (d, 1H), 3.20 (m, 4H), 2.2 (m, 4H)

Melting point: 180-82 °C

25 **Example 6**

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide

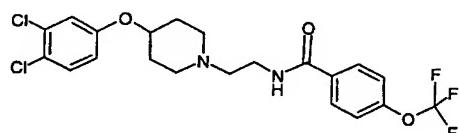
Prepared by the same method as Example 2 using 4-methoxybenzoic without the addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid (0.11g).

5

MS: ESI 423.12 (M+H)

¹H NMR: δ(DMSO) 8.42 (t, 1H), 7.81 (m, 2H), 7.49 (d, 1H), 7.25 (d, 1H), 6.98 (s, 3H), 4.4 (m, 1H), 3.8 (s, 3H), 3.35 (q, 2H), 2.73 (m, 2H), 2.47 (m, 2H), 2.30 (m, 2H), 1.91 (m, 2H), 1.60 (m, 2H)

10 Melting point: 110-12 °C

Example 7**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethoxy)benzamide hydrochloride**

15

Prepared by the same method as Example 2 using 4-trifluoromethoxybenzoic acid to give the titled product as a solid (0.19g).

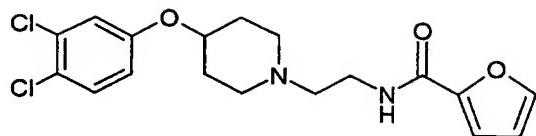
MS: ESI 477 (M+H)

¹H NMR: δ(DMSO) 10.5 (bs, 1H), 9.06 (m, 1H), 8.07 (dd, 2H), 7.55 (t, 1H), 7.49 (d, 2H), 7.36 (dd, 1H), 7.10-7.02 (m, 1H), 4.72 (m, 1H), 3.70 (m, 3H), 3.47 (d, 1H), 3.14 (m, 2H), 2.25 (m, 2H), 2.02 (m, 2H)

Melting point: 184-187 °C

25 **Example 8**

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide hydrochloride



Prepared by the same method as Example 2 using furan-2-carboxylic acid to give the titled product as a solid (0.14g).

5

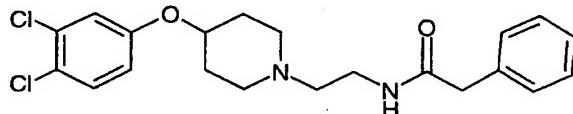
MS: ESI 383.09 (M+H)

¹H NMR: δ(DMSO) 10.43 (bm, 1H), 8.76 (t, 1H), 7.87 (s, 1H), 7.55 (t, 1H), 7.36 (dd, 1H), 7.21 (d, 1H), 7.06 (m, 1H), 6.64 (dd, 1H), 4.83-4.61 (m, 1H); 3.65 (m, 3H), 3.45 (d, 1H), 3.08 (m, 4H), 2.1 (m, 4H)

10 Melting point: 225-28 °C

Example 9

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide hydrochloride



15

Prepared by the same method as Example 2 using phenylacetic acid to give the titled product as a solid (0.12g).

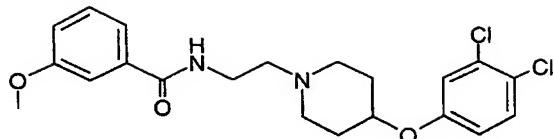
MS: ESI 407 (M+H)

¹H NMR: δ(DMSO) 10.28 (bm, 1H), 8.46 (bm, 1H), 7.56 (t, 1H), 7.3 (m, 6H), 7.10 (m, 1H), 4.81/4.58 (m, 1H), 3.58 (d, 1H), 3.46 (m, 4H), 3.10 (m, 4H), 2.15 (m, 5H)

Melting point: 135-38 °C

Example 10

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride



The product of Example 1 step (iv) (2.0g) was dissolved in dichloromethane (490ml), triethylamine (1.85ml) and 3-methoxybenzoyl chloride (0.66g) were added. After 72 hours at room temperature, water was added, the organic phase separated, dried and concentrated to a gum. The product was dissolved in dichloromethane and treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.88g).

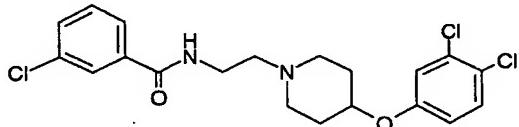
MS: ESI 423.12 (M+H)

¹H NMR: δ(DMSO) 10.6-10.5 (m, 1H), 9.92 (s, 1H), 7.54 (m, 3H), 7.38 (m, 2H), 10 7.08 (m, 2H), 4.84/4.62 (m 1H), 3.82 (s, 3H), 3.45 (m, 8H), 2.27 (m, 4H).

Melting point: 72-73 °C

Example 11

3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide hydrochloride



The product of Example 1 step (iv) (0.15g) was dissolved in DMF (3ml), N,N-di-isopropylethylamine (0.3ml) and 3-chlorobenzoyl chloride (0.054ml) were added. After 2 hours at room temperature, water and ethyl acetate were added, the organic phase separated dried and concentrated. The residue was purified by chromatography (dichloromethane : methanol, 95:5) to give an oil which was dissolved in ether and 1.0M ethereal hydrogen chloride solution added to give the titled product as a solid (0.12g).

MS: ESI 427.07 (M+H)

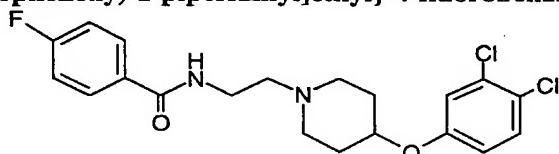
¹H NMR: δ(DMSO) 8.42 (t, 1H), 7.94-7.84 (m, 2H), 7.49 (d, 1H), 7.29 (m, 3H),
6.98 (dd, 1H), 4.44 (m, 1H), 3.36 (m, 2H), 2.74 (m, 2H), 2.48 (m, 2H), 2.29 (bt, 2H),
1.92 (m, 2H), 1.60 (m, 2H)

Melting point: 118 °C

5

Example 12

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-fluorobenzamide



Prepared by the same method as Example 11 using 4-fluorobenzoyl chloride without the
10 addition of 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid
(0.1g).

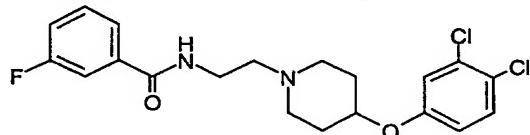
MS: ESI 411.10 (M+H)

¹H NMR: δ(DMSO) 10.46 (bs, 1H), 9.04 (s, 1H), 7.98 (s, 1H), 7.90 (d, 1H), 7.58 (m, 3H),
15 7.36 (dd, 1H), 7.05 (m, 1H), 4.84/4.60 (m, 1H), 3.69 (m, 3H), 3.48 (bd, 1H), 3.20 (m, 4H),
2.15 (m, 4H)

Melting point: 192 °C

Example 13

20 N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-fluorobenzamide hydrochloride



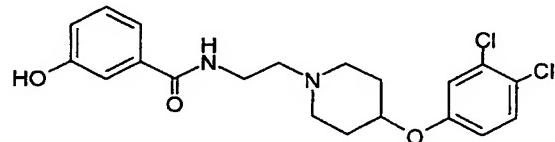
Prepared by the same method as Example 11 using 3-fluorobenzoyl chloride to give the
titled product as a solid (0.09g).

25 MS: ESI 411.10 (M+H)

¹H NMR: δ(DMSO) 10.67 (bs, 1H), 9.06 (s, 1H), 7.80 (m, 2H), 7.55 (m, 2H), 7.40 (m, 2H), 7.05 (m, 1H), 4.84/4.63(m, 1H), 3.70 (m, 3H), 3.28 (m, 3H), 2.20 (m, 4H)
 Melting point: 225 °C

5 **Example 14**

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-hydroxybenzamide hydrochloride



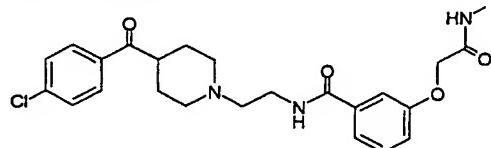
The product of Example 10 (0.15g) was dissolved in dichloromethane (10ml) and a
 10 solution of 1.0M BBr₃ in dichloromethane (4ml) added. After 16 hours at room
 temperature the solvent was removed by evaporation, methanol was added and the solution
 concentrated. The residue was dissolved in 2M aqueous HCl solution, concentrated to
 dryness and the residue triturated under ether to give the titled product as a solid (0.1g).

15 **MS: ESI 409.10 (M+H)**

¹H NMR: δ(DMSO) 9.98-9.4 (bs, 2H), 8.71 (t, 1H), 7.6 (dd, 1H), 7.4-7.2 (m, 4H),
 7.05 (m, 1H), 6.95 (dd, 1H), 4.65 (m, 1H), 3.40 (m, 8H), 2.0 (m, 4H)
 Melting point: 83-4 °C

20 **Example 15**

N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride



25 **(i) [1-(2-Aminoethyl)-4-piperidinyl](4-chlorophenyl)methanone trifluoroacetate**

To a solution of (4-chlorophenyl)(4-piperidinyl)methanone hydrochloride (2.5g) and tert-butyl 2-bromoethylcarbamate (2.1g) in DMF was added triethylamine (2.9g), after 72 hours at room temperature water and ether were added. The organic phase was separated, dried and concentrated. The residue was dissolved in dichloromethane (40 ml), trifluoroacetic acid (10ml) added and the solution left for 20 hours. Evaporation of the solvent gave a sticky solid which was triturated under ether to give the sub-titled product as a solid (2.5g).

(ii) N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-3-methoxybenzamide hydrochloride

The product of step (i) (2.5g) was dissolved in dichloromethane (20ml), triethylamine (0.75ml) and 3-methoxybenzoyl chloride (0.276g) were added. After 16 hours, water was added, the organic phase separated, dried and concentrated to a gum. Purification by chromatography (ethyl acetate) gave a gum, which was treated with 1.0M ethereal hydrogen chloride solution to give the sub-titled product as a solid (0.3g).

15

MS: ESI 401.16 (M+H)

¹H NMR: δ(DMSO) 10.3 (bm, 1H), 8.95 (t, 1H), 8.0 (m, 2H), 7.6 (m, 2H), 7.5 (m, 2H), 7.4 (t, 1H), 7.05 (m, 1H), 3.8 (s, 3H), 3.68 (m, 4H), 3.28 (m, 5H), 2.0 (m, 4H).

Melting point: 196-7 °C

20

(iii) N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-3-hydroxybenzamide hydrochloride

Prepared by the method of Example 14 using the product of step (ii) above (0.24g) to give the sub-titled product as a solid (0.20g).

25

MS: ESI 387.14 (M+H)

¹H NMR: δ(DMSO) 8.62 (t, 1H), 8.05 (dd, 2H), 7.6 (dd, 2H), 7.25 (m, 3H), 6.95 (m, 1H), 4.26 (m, 9H), 2.0 (m, 4H)

Melting point: 90-91 °C

30

(iv) N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-3-[2-(methylamino)-2-oxoethoxy]benzamide hydrochloride

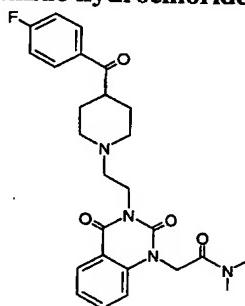
The product of step (iii) above (0.10g) was dissolved in DMF (3ml), Cs₂CO₃ (0.23g) and 2-chloro-N-methylacetamide (0.26g) were added and the mixture heated at 80° C for 16 hours. The mixture was cooled to room temperature, water and ethyl acetate were added and the organic phase separated. Evaporation of the solvent gave a gum which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.05g).

MS: ESI 458.18 (M+H)

¹H NMR: δ(DMSO) 10.6-10.2 (bm, 1H), 8.95 (bm, 1H), 8.1 (m, 2H), 7.55 (m, 8H), 7.14 (bd, 1H), 4.54 (s, 2H), 4.0 (m, 1H), 3.4 (m, 8H), 2.65 (d, 3H), 2.0 (m, 4H)
Melting point: 69-70 °C

Example 16

2-[3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl]-N,N-dimethylacetamide hydrochloride



3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4(1H,3H)-quinazolinenedione was dissolved in DMF (5ml) and NaH (60% dispersion in mineral oil) added. After 0.5 hours, 2-chloro-N,N-dimethylacetamide was added and the solution stirred at room temperature for 16 hours. Water and ethyl acetate were added, the organic phase separated, dried and concentrated to an oil. Purification by chromatography (dichloromethane : methanol 95:5) gave an oil which was treated with 1.0 M ethereal hydrogen chloride solution to give the titled product as a solid(0.015g).

MS: ESI 481.22 (M+H)

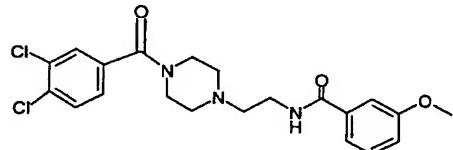
¹H NMR: δ(DMSO) 8.08 (m, 3H), 7.76 (t, 1H), 7.40 (t, 2H), 7.32 (m, 2H), 5.05 (s, 2H),
 4.36 (m, 1H), 3.76 (m, 3H), 3.39 (m, 2H), 3.15 (s, 3H), 2.87 (s, 3H), 2.02 (m, 2H),
 1.81 (m, 2H), 1.28 (m, 2H)

Melting point: 245-246 °C

Example 17

N-[2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl]-3-methoxybenzamide

hydrochloride



(i) tert-Butyl 2-(1-piperazinyl)ethylcarbamate

A mixture of benzaldehyde (21g) and 1-(2-aminoethyl)piperazine (25.8g) was stirred and heated under a Dean and Stark water separator for 20 hours. The cooled solution was

treated portionwise with di-tert-butyl dicarbonate (48g), stirred for 72 hours and concentrated. The residue was treated with 1M aqueous KHSO₄ solution (220ml), stirred for 24 hours, ether was added and the organic phase separated. The aqueous phase was treated with 2M NaOH solution, dichloromethane was added and the organic phase separated. The combined organic phase was washed with brine, dried and concentrated to give the sub-titled product as an oil (30g).

MS: APCI(+ve) 230 (M+H)

¹H NMR δ (CDCl₃) 3.43 (t, 4H), 2.8 (t, 2H), 2.45 (m, 6H), 1.5 (s, 9H).

(ii) tert-Butyl 2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethylcarbamate

The product from step (i) above (3g) was dissolved in pyridine (12ml), 3,4-dichlorobenzoyl chloride (2.05g) was added and the mixture stirred at room temperature for 18 hours. A

solid was collected by filtration and purified by chromatography (dichloromethane : methanol : 0.880 NH₄OH, 90:9:1) to give the sub-titled product as an oil (3.59g).

MS: APCI(+ve) 364(M+H)

5 ¹H NMR δ (CDCl₃) 7.33 (m, 3H), 7.04 (m, 1H), 6.76 (bs, 1H), 3.86 (s, 3H), 3.55 (q, 2H),
3.45 (t, 4H), 2.61 (t, 3H), 2.46 (t, 4H), 1.46 (s, 9H)

(iii) [4-(2-Aminoethyl)-1-piperazinyl](3,4-dichlorophenyl)methanone trifluoroacetate

The product from step (ii) above (3.3g) was dissolved in dichloromethane (50ml) and
10 trifluoroacetic acid (10ml) added. After 16 hours at room temperature the solvent was removed to give the sub-titled product as an oil (5.9g).

MS: APCI(+ve) 264(M+H)

15 (iv) N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride

The product from step (iii) above (0.15g) was dissolved in pyridine (2ml) and 3-methoxybenzoyl chloride (0.064g) added. After 16 hours at room temperature, water and ethyl acetate were added, the organic phase separated, dried and concentrated to an oil.
20 Purification by chromatography (dichloromethane : methanol, 95:5) gave an oil which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.043g).

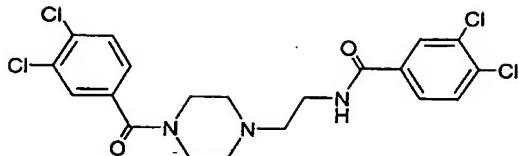
MS: ESI 436.12 (M+H)

25 ¹H NMR: δ(DMSO) 8.8 (bt, 1H), 7.34 (m, 2H), 7.43 (m, 4H), 7.14(m, 1H), 3.82(s, 3H),
3.48 (m,12H)

Melting point: 230 °C

Example 18

30 **3,4-Dichloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}benzamide**



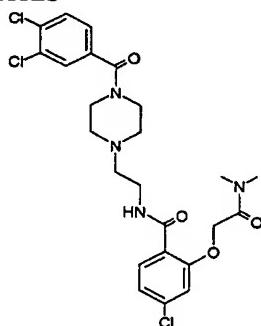
A solution of benzaldehyde (5.3g) and 1-(2-aminopiperazine) (6.45g) in toluene (100ml) was heated under a Dean and Stark water separator for 4 hours. The solution was cooled to room temperature and triethylamine (5.05g) added. A solution of 3,4-dichlorobenzoyl chloride (10.48g) in toluene (50ml) was added dropwise, the solution stirred at room temperature for 18 hours and water added. The organic phase was separated, dried and concentrated to a residue which was treated with 1N aqueous KHSO₄ solution (65ml). The mixture was stirred vigorously for 4 hours, ether was added, the aqueous phase separated and NaOH added. CHCl₃ was added, the organic phase separated, dried and concentrated to a gum. Purification by chromatography (dichloromethane : triethylamine, 95:5) gave the titled product as a foam (0.25g).

MS: ESI 474.03 (M+H)

¹H NMR: δ(DMSO) 8.8 (bt, 1H), 7.34 (m, 2H), 7.43 (m, 4H), 7.14 (m, 1H), 3.82 (s, 3H), 15 3.48 (m, 12H)

Example 19

4-Chloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide hydrochloride



20

The product of Example 26 step (ii) (0.3g), 3,4-dichlorobenzoyl chloride (0.1g) and triethylamine (0.15g) were dissolved in dichloromethane (15ml). After 20 hours at room

temperature water was added, the organic phase separated, dried and evaporated to give a gum. Purification by chromatography (dichloromethane : methanol, 20:1) gave a solid which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.1g).

5

MS: ESI 541.11 (M+H)

¹H NMR δ(DMSO-D₆) 9.54 (t, 1H), 7.91 (d, 1H), 7.74 (m, 2H), 7.43 (m, 2H),

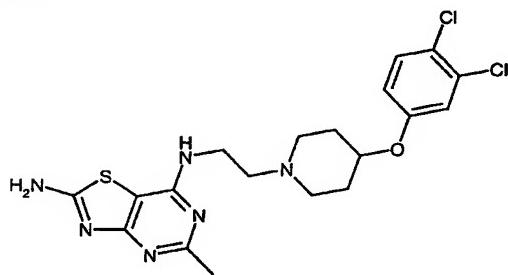
7.18 (d, 1H), 5.12 (s, 2H), 3.2-3.8 (m, 12H), 2.99 (s, 3H), 2.88 (s, 3H).

Melting point: 226-7 °C.

10

Example 20

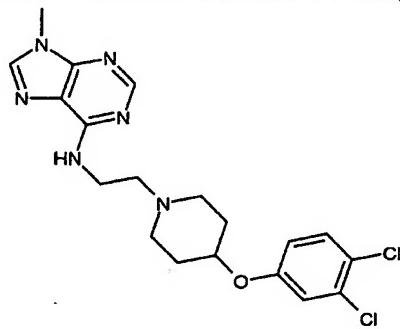
N~7~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine



15 MS: APCI(+ve) 453 (M+1)

Example 21

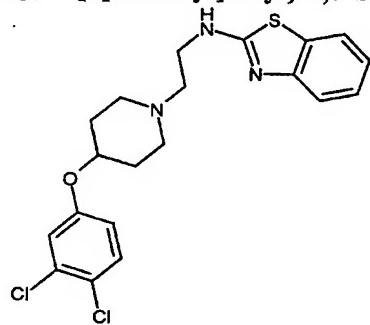
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-9-methyl-9H-purin-6-amine



MS: APCI(+ve) 421 (M+1)

Example 22

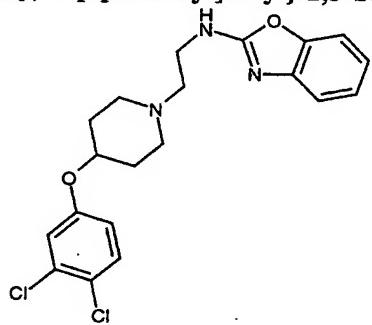
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-1,3-benzothiazol-2-amine



MS: APCI(+ve) 422 (M+1)

Example 23

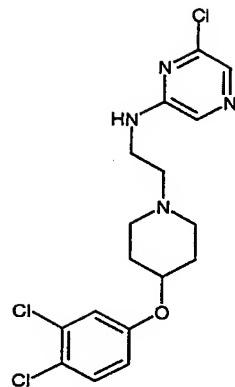
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-1,3-benzoxazol-2-amine



MS: APCI(+ve) 406 (M+1)

Example 24

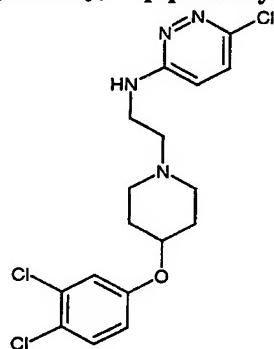
6-Chloro-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-2-pyrazinamine



MS: APCI(+ve) 403 (M+1)

Example 25

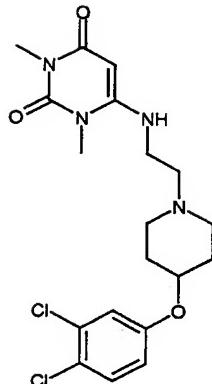
- 5 **6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-pyridazinamine**



MS: APCI(+ve) 403 (M+1)

Example 26

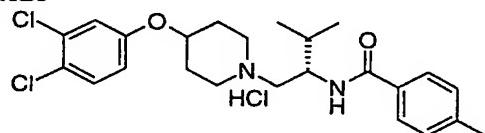
- 10 **6-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione**



MS: APCI(+ve) 427 (M+1)

Example 27

- 5 N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-benzamide, hydrochloride



(i) N-{1-[4-(3,4-Dichlorophenoxy)-piperidine-1-carbonyl]-2-methyl-propyl}-acetamide

N-Boc Valine (1.13g) was dissolved in dichloromethane (5 ml) and EDC (0.99g) added, after 5 min the product according to Example 1 step (ii) (1.44g) in dichloromethane (5 ml) was added in one portion. After 3 hours at room temperature, aqueous sodium bicarbonate solution and ethyl acetate were added. The organic phase was separated and the solvent removed to give the sub-titled compound as an oil (1.57 g) which was used in the next step without further purification.

15

(ii) 2-amino-1-[4-(3,4-dichlorophenoxy)-piperidine-1-yl]-3-methyl-butan-1-one

The product of step (i) (1.57 g) was dissolved in dichloromethane (14 ml) and trifluoroacetic acid (4 ml) added. After 2 hours at room temperature the solvent was removed, ethyl acetate and 2N aqueous NaOH solution were added to give pH 8.0. The organic phase was separated and concentrated to give the sub-titled product as an oil (1.24 g) which was used in the next step without further purification.

(iii) 1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propylamine

The product of step (ii) (1.12g) was dissolved in THF (10 ml) and Borane/THF complex (22.7 ml) added. The mixture was heated under reflux for 2 hours and cooled. The solvent was evaporated, the product dissolved in methanol (5ml) and 50% aqueous HCl solution added. The mixture was heated to 70 °C for 1 hour and cooled to room temperature. The solvent was removed, ethyl acetate and 2N aqueous NaOH solution were added to give pH 9.0. The organic phase was separated and the solvent evaporated to give the sub-titled compound as an oil (0.98 g) which used without further purification.

10

(iv) N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-benzamide, hydrochloride

The product of step (iii) (0.2g) was dissolved in dichloromethane (5ml), triethylamine (0.126 ml) and 4-methylbenzoyl chloride (0.097 ml) were added. After 2 hours at room temperature, ethyl acetate and aqueous NaHCO₃ solution were added, the organic phase separated and the solvent removed to leave an oil. Purification by reverse phase HPLC (with a gradient eluent system (25% MeCN/NH₄OAc_{aq} (0.1%) to 95% MeCN//NH₄OAc_{aq} (0.1%)) gave a gum. Addition of 1.0M ethereal hydrogen chloride solution gave the titled product as a solid (0.104 g).

20

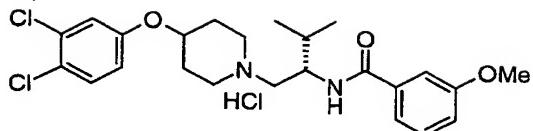
Melting point: 131-132°C

MS: ESI 450 (M+H)

¹H NMR: δ(DMSO) 8.45 (t, 1H), 7.00-7.90 (m, 7H), 4.79 (br s, 1H), 4.24-4.30 (m, 1H), 3.10-3.42 (m, 5H), 2.36 (s, 3H), 1.88-2.40 (m, 5H), 0.92 (t, 6H)

25

Example 28**N-{1-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-methoxy-benzamide, hydrochloride**



The product according to Example 27 step (iii) dissolved in dichloromethane (4 ml), triethylamine (0.090 ml) and 3-methoxybenzoyl chloride (0.077 ml) were added. After 2 hours at room temperature, NaHCO₃ was added, the product extracted with ethyl acetate, the combined organic extracts dried with Na₂SO₄ and concentrated. Purification with reverse phase HPLC (with a gradient eluent system (25% MeCN/NH₄OAc_{aq} (0.1%) to 95% MeCN/NH₄OAc_{aq} (0.1%)) gave a gum. The product was dissolved in methanol and treated with 1.0M ethereal Hydrogen chloride solution to give the product as a solid (0.045 g).

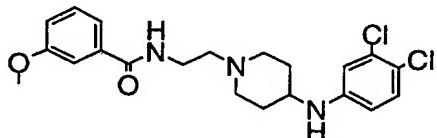
10

MS: ESI 465 (M+H)

¹H NMR: δ(DMSO) 8.58-8.63 (m, 1H), 7.01-7.58 (m, 6H), 4.80 (br s, 1H), 4.23-4.59 (m, 1H), 3.83 (s, 3H), 3.04-3.60 (m, 4H), 1.89-2.14 (m, 5H), 0.85 (m, 6H)

15 **Example 29**

N-[2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl]-3-methoxybenzamide dihydrochloride



(i) **tert-Butyl 4-(3,4-dichloroanilino)-1-piperidinecarboxylate**

20 A solution of 3,4-dichloroaniline (5g), *N*-tert-butoxycarbonyl-4-piperidone (11.7g), sodium triacetoxyborohydride (19.7g) and acetic acid (7ml) in dichloroethane (150ml) was stirred for 16 hours. 2M NaOH solution and ether were added, the organic phase separated, dried and concentrated. The residue was triturated under an isohexane : ethyl acetate, 4:1 mixture and the sub-titled product collected as a solid (7.25g).

25

MS: APCI(+ve) 345 (M+H)

¹H NMR: δ(DMSO) 7.23 (d, 1H), 6.77 (d, 1H), 6.57 (dd, 1H), 5.99 (d, 1H), 3.85 (bd, 2H), 3.40 (m, 1H), 2.90 (bm, 2H), 1.85 (m, 2H), 1.39 (s, 9H), 1.19 (m, 2H)

(ii) **N-(3,4-Dichlorophenyl)-4-piperidinamine trifluoroacetate**

5 The product of step (i) above (6.5g) was dissolved in dichloromethane (75ml) and trifluoroacetic acid (25ml) added. After 72 hours at room temperature the solution was evaporated and the residue triturated under ether to give the sub-titled product as a solid (6.3g).

10 MS: APCI(+ve) 245/7 (M+H)

¹H NMR: δ(DMSO) 8.65 (bs, 1H), 8.50 (bs, 1H), 7.26 (d, 1H), 6.81 (d, 1H), 6.60 (dd, 1H), 6.19 (bs, 1H), 3.53 (bs, 1H), 3.30 (m, 2H), 3.0 (m, 2H), 2.02 (m, 2H), 1.50 (m, 2H)

15 (iii) **tert-Butyl 2-[4-(3,4-dichloroanilino)-1-piperidinyl]ethylcarbamate**

The product from step (ii) above (2.0g), N-tert-butoxycarbonyl-2-bromoethanamine (1.0g) and N,N-di-isopropylethylamine (3.7ml) were dissolved in DMF (25ml) and stirred for 16 hours. Water and ethyl acetate were added, the organic phase separated, dried and evaporated to give a gum. Purification by chromatography (dichloromethane : methanol, 20 95:5) gave the sub-titled product as a solid (1.25g).

MS: APCI(+ve) 388/90 (M+H)

¹H NMR: δ(DMSO) 7.22 (d, 1H), 6.73 (d, 1H), 6.62 (t, 1H), 6.54 (dd, 1H) 5.94 (d, 1H), 3.17 (m, 1H), 3.02 (m, 2H), 2.77 (bd, 2H), 2.31 (t, 3H), 2.06 (t, 2H), 1.84 (bd, 2H), 25 1.35 (m, 11H)

(iv) **1-(2-Aminoethyl)-N-(3,4-dichlorophenyl)-4-piperidinamine trifluoroacetate**

The product from step (iii) above (1.2g) was dissolved in dichloromethane (30ml) and trifluoroacetic acid (10ml) added. After 72 hours at room temperature the reaction mixture

was evaporated and residue triturated under ether to give the sub-titled product as a solid (1.6g).

MS: APCI(+ve) 288/90 (M+H)

5

(v) N-{2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride

The product of step (iv) above (0.5g) and triethylamine (1.1ml) were dissolved in DMF (10ml), 3-methoxybenzoylchloride (0.11ml) was added dropwise. After 2 hours, water and ethyl acetate were added, the organic phase separated, dried and evaporated. Purification of the residue by chromatography (dichloromethane : methanol, 95:5) gave an oil which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.15g).

15 MS: ESI 422.14 (M+H)

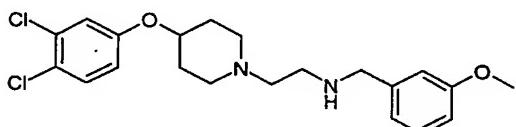
¹H NMR: δ(DMSO) 10.44 (bs, 1H), 8.93 (t, 1H) 7.51 (m, 2H), 7.40 (t, 1H), 7.26 (d, 1H), 7.11 (dd, 1H), 6.81 (d, 1H), 6.60 (dd, 1H), 3.82 (s, 3H), 2.68 (m, 4H), 3.25 (m, 5H), 2.09 (bd, 2H), 1.76 (m, 2H)

Melting point: 170 °C

20

Example 30

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-(3-methoxybenzyl)amine dihydrochloride



25 A suspension of the product of Example 1 step (iv) (0.11g) in a mixture of DMF (1.5ml) and 1,2-dichloroethane (3ml) was stirred under an atmosphere of nitrogen. Sodium triacetoxyborohydride (0.097g), 3-methoxybenzaldehyde (0.041g) and triethylamine (0.046g) were added and the mixture stirred for 18 hours at room temperature. Chloroform

and aqueous NaHCO₃ solution were added, the organic phase separated, dried and concentrated to a gum. Purification by chromatography (chloroform : triethylamine : methanol, 89 :10:1) gave an oil which was treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.067g).

5

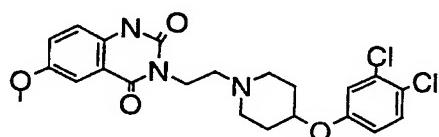
MS: ESI 409.14 (M+H)

¹H NMR: δ(DMSO) 7.50 (d, 1H), 7.30 (m, 3H), 7.12 (d, 1H), 7.03 (dd, 1H), 6.97 (dd, 1H), 4.71 (bm, 1H), 4.18 (s, 2H), 3.80 (s, 3H), 3.45 (bm, 4H), 2.23 (m, 6H), 2.04 (m, 2H), Melting point: 247-51 °C

10

Example 31

3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-quinazolininedione



- 15 (i) 2-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide

Prepared by the method of Example 2 using the product from Example 1 step (iv) (1.0g) and 2-amino-5-methoxybenzoic acid (0.418g) without the addition of 1.0M ethereal hydrogen chloride solution to give an oil which was purified by chromatography

- 20 (dichloromethane : methanol, 95:5) to give the sub-titled product as an oil (0.82g).

MS: APCI(+ve) 438 (M+H)

- (ii) 3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-quinazolininedione

The product of step (i) above was dissolved in toluene (10ml). A solution of phosgene 2.0M in toluene (10ml) was added, the solution heated under reflux for 1 hour and cooled. Ethyl acetate and aqueous NaHCO₃ solution were added, the organic phase separated,

dried and concentrated to leave a residue which was purified by chromatography (dichloromethane : methanol, 95:5). The titled product was obtained as a solid (0.11g).

MS: ESI 464.11 (M+H)

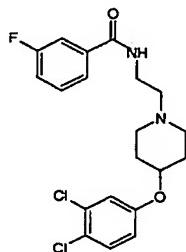
5 ^1H NMR: δ (DMSO) 7.49 (dd, 1H), 7.36 (d, 1H), 7.30 (dd, 1H), 7.24 (d, 1H), 6.98 (dd, 1H), 4.44 (m, 1H), 4.03 (t, 3H), 3.80 (s, 3H), 2.76 (m, 2H), 2.32 (m, 2H), 1.89 (m, 2H), 1.57 (m, 2H)

Melting point: 190 °C

- 10 The compounds of following Examples 32 to 125 were prepared by methods analogous to the method of Example 10.

Example 32

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-fluorobenzamide

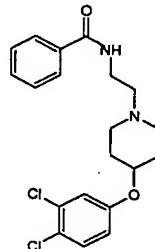


15

MS: APC1 (+ve) BP 411

Example 33

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]benzamide

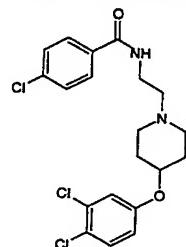


20

MS: APC1 (+ve) BP 393

Example 34

4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide

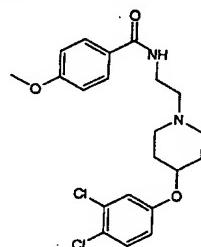


5

MS: APC1 (+ve) BP 429

Example 35

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide

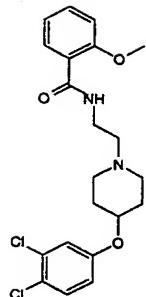


10

MS: APC1 (+ve) BP 423

Example 36

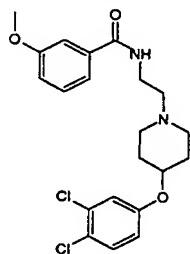
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxybenzamide



MS: APC1 (+ve) BP 423

Example 37

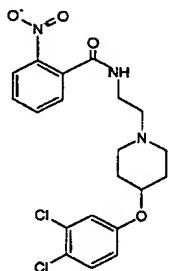
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide



MS: APC1 (+ve) BP 423

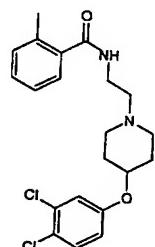
Example 38

- 10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-nitrobenzamide

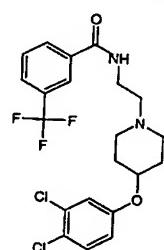


MS: APC1 (+ve) BP 438

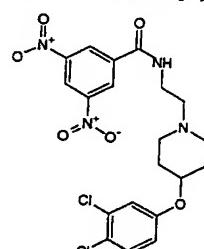
Example 39

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methylbenzamide

MS: APC1 (+ve) BP 407

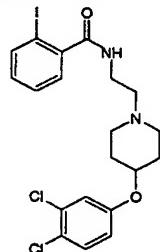
5 **Example 40****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide**

MS: APC1 (+ve) BP 461

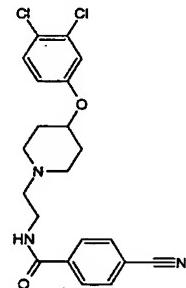
10 **Example 41****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-dinitrobenzamide**

MS: APC1 (+ve) BP 483

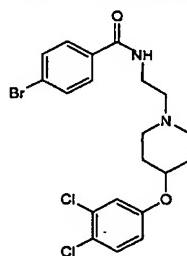
15 **Example 42**

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-iodobenzamide

MS: APC1 (+ve) BP 519

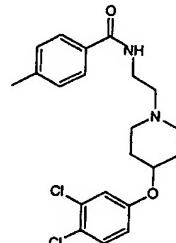
5 Example 43**4-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 418

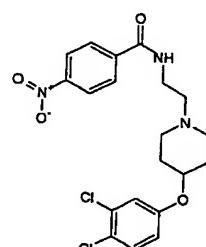
10 Example 44**4-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 473

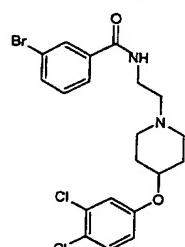
15 Example 45

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-methylbenzamide

MS: APC1 (+ve) BP 407

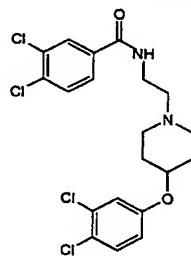
5 **Example 46****N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-nitrobenzamide**

MS: APC1 (+ve) BP 438

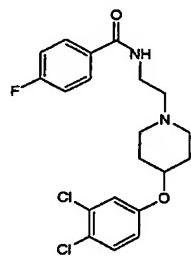
10 **Example 47****3-Bromo-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]benzamide**

MS: APC1 (+ve) BP 473

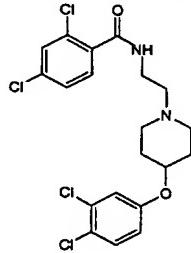
15 **Example 48**

3,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide

MS: APC1 (+ve) BP 463

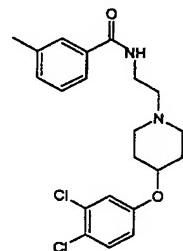
5 **Example 49****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide**

MS: APC1 (+ve) BP 411

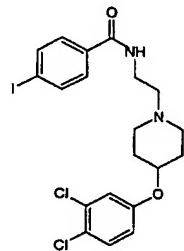
10 **Example 50****2,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 463

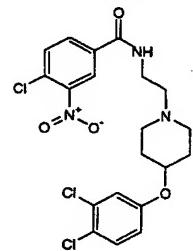
15 **Example 51**

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methylbenzamide

MS: APC1 (+ve) BP 407

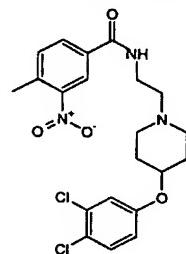
5 **Example 52****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-iodobenzamide**

MS: APC1 (+ve) BP 519

10 **Example 53****4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-nitrobenzamide**

MS: APC1 (+ve) BP 472

15 **Example 54**

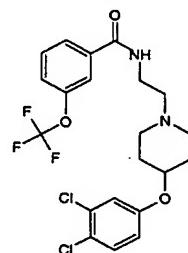
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-methyl-3-nitrobenzamide

MS: APC1 (+ve) BP 452

5 **Example 55****N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-fluoro-5-(trifluoromethyl)benzamide**

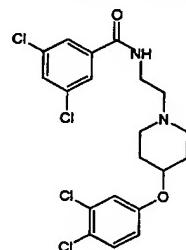
MS: APC1 (+ve) BP 479

10

Example 56**N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-(trifluoromethoxy)benzamide**

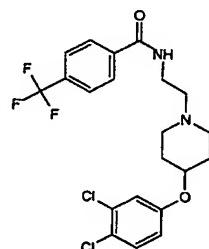
MS: APC1 (+ve) BP 477

15

Example 57**3,5-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

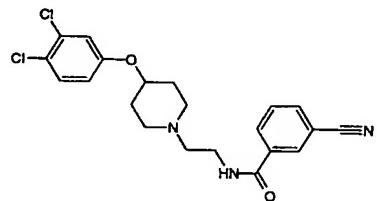
MS: APC1 (+ve) BP 463

5

Example 58**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)benzamide**

MS: APC1 (+ve) BP 461

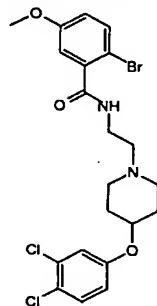
10

Example 59**3-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

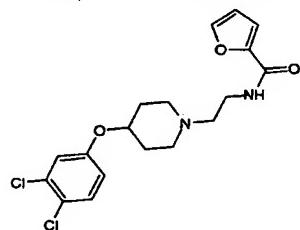
MS: APC1 (+ve) BP 418

15

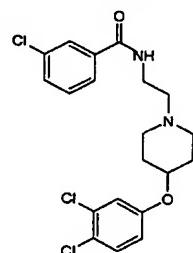
Example 60

2-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide

MS: APC1 (+ve) BP 503

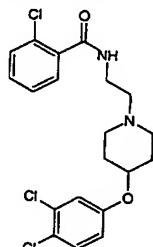
5 Example 61**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide**

MS: APC1 (+ve) BP 383

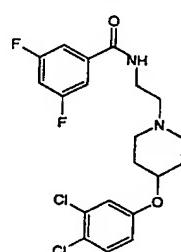
10 Example 62**3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 427

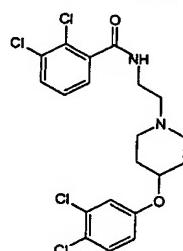
15 Example 63

2-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide

MS: APC1 (+ve) BP 429

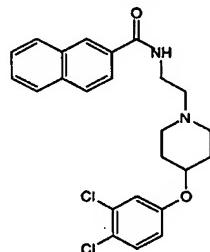
5 **Example 64****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-difluorobenzamide**

MS: APC1 (+ve) BP 429

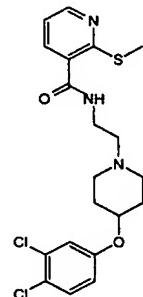
10 **Example 65****2,3-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 463

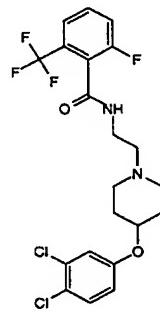
15 **Example 66**

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-naphthamide

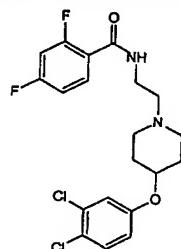
MS: APC1 (+ve) BP 442

5 **Example 67****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide**

MS: APC1 (+ve) BP 440

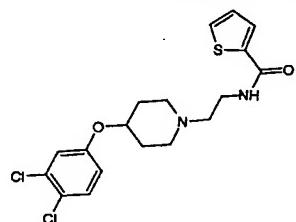
10 **Example 68****N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-6-(trifluoromethyl)benzamide**

MS: APC1 (+ve) BP 479

Example 69**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-difluorobenzamide**

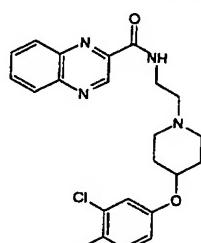
5

MS: APC1 (+ve) BP 429

Example 70**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-thiophenecarboxamide**

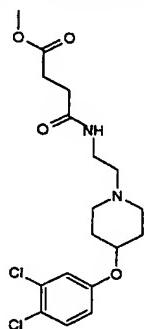
10

MS: APC1 (+ve) BP 399

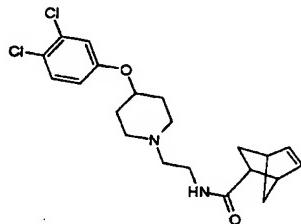
Example 71**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide**

15

MS: APC1 (+ve) BP 445

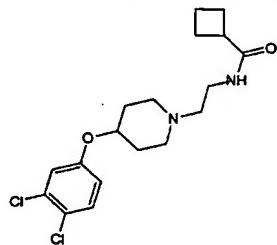
Example 72**Methyl 4-({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)-4-oxobutanoate**

5 MS: APC1 (+ve) BP 403

Example 73**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide**

10

MS: APC1 (+ve) BP 409

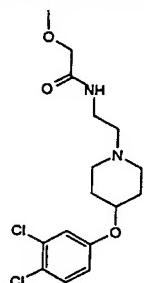
Example 74**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclobutanecarboxamide**

15

MS: APC1 (+ve) BP 371

Example 75

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxyacetamide

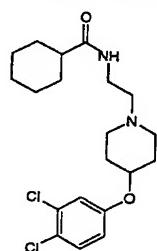


5

MS: APC1 (+ve) BP 361

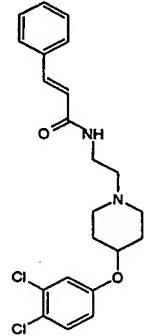
Example 76

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclohexanecarboxamide



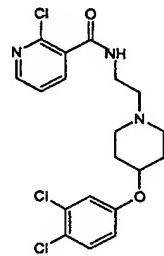
10

MS: APC1 (+ve) BP 399

Example 77**(E)-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide**

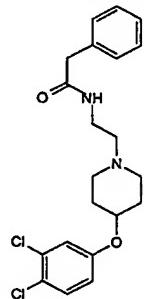
MS: APC1 (+ve) BP 419

5

Example 78**2-Chloro-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}nicotinamide**

MS: APC1 (+ve) BP 430

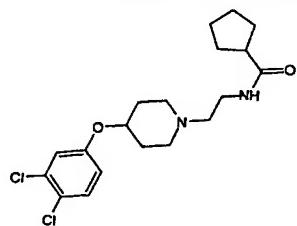
10

Example 79**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide**

MS: APC1 (+ve) BP 407

Example 80

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclopentanecarboxamide

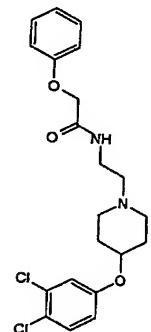


5

MS: APC1 (+ve) BP 385

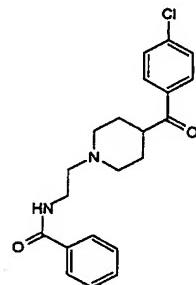
Example 81

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenoxyacetamide



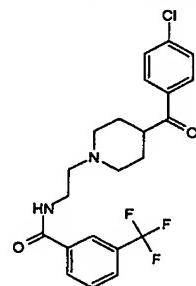
10

MS: APC1 (+ve) BP 423

Example 82**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}benzamide**

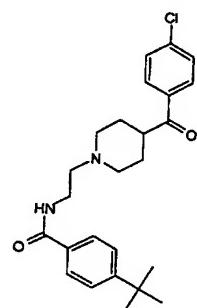
MS: APC1 (+ve) BP 371

5

Example 83**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide**

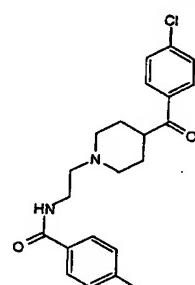
MS: APC1 (+ve) BP 439

10

Example 84**4-(tert-Butyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}benzamide**

MS: APC1 (+ve) BP 427

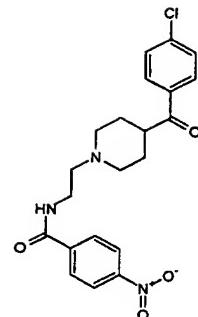
5

Example 85**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methylbenzamide**

MS: APC1 (+ve) BP 385

10

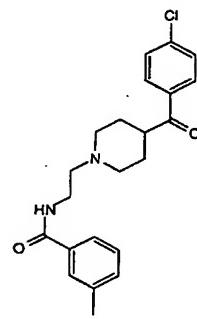
Example 86**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-nitrobenzamide**



MS: APC1 (+ve) BP 416

Example 87

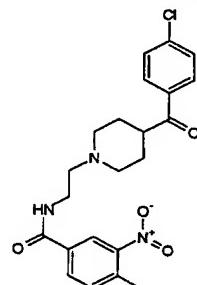
- 5 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methylbenzamide



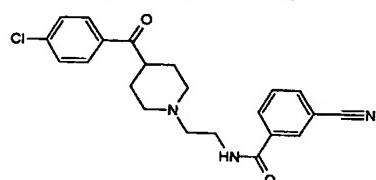
MS: APC1 (+ve) BP 385

Example 88

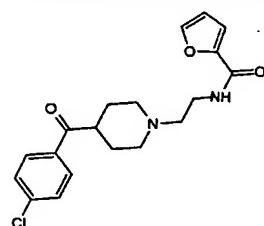
- 10 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide



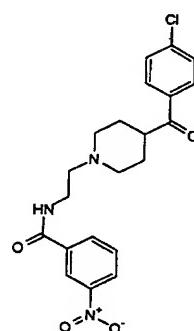
MS: APC1 (+ve) BP 430

Example 89**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-cyanobenzamide**

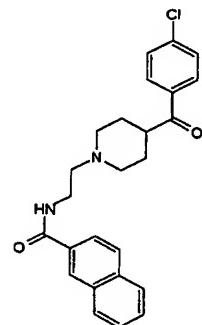
5 MS: APC1 (+ve) BP 396

Example 90**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-furamide**

10 MS: APC1 (+ve) BP 361

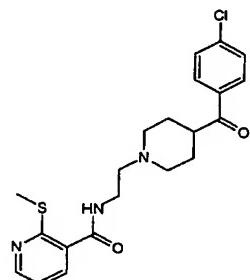
Example 91**N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-nitrobenzamide**

15 MS: APC1 (+ve) BP 416

Example 92**N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-2-naphthamide**

MS: APC1 (+ve) BP 421

5

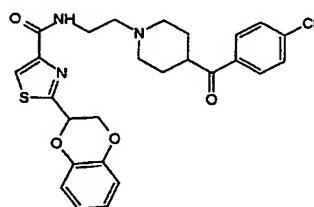
Example 93**N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-2-(methylsulfanyl)nicotinamide**

MS: APC1 (+ve) BP 418

10

Example 94

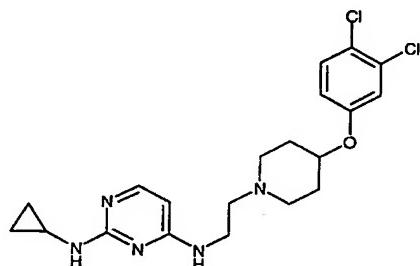
N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1,3-thiazole-4-carboxamide



5 MS: APC1 (+ve) BP 512

Example 95

N~2~-Cyclopropyl-N~4~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine



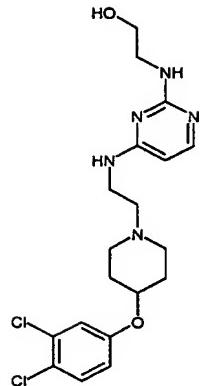
10

MS: APCI(+ve) 422 (M+1)

Example 96

2-{{[4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl]amino}-1-ethanol

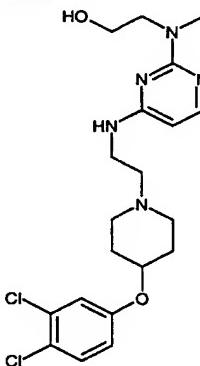
15



MS: APCI(+ve) 426 (M+1)

Example 97

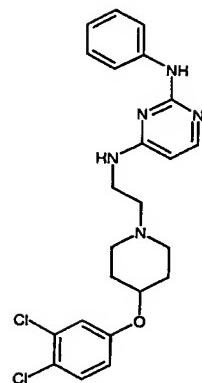
- 5 2-[(4-(2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl)amino)-2-pyrimidinyl](methyl)amino]-1-ethanol



MS: APCI(+ve) 440 (M+1)

10 **Example 98**

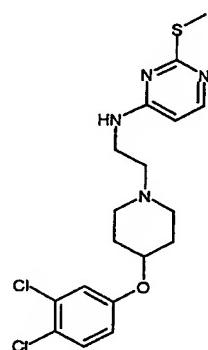
- N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~-phenyl-2,4-pyrimidinediamine



MS: APCI(+ve) 458 (M+1)

Example 99

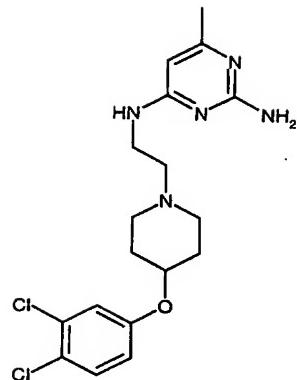
- 5 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)-4-pyrimidinamine**



MS: APCI(+ve) 413 (M+1)

10 **Example 100**

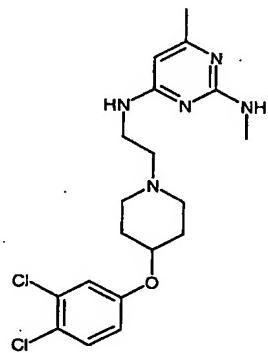
- N-{4-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2,4-pyrimidinediamine**



MS: APCI(+ve) 396 (M+1)

Example 101

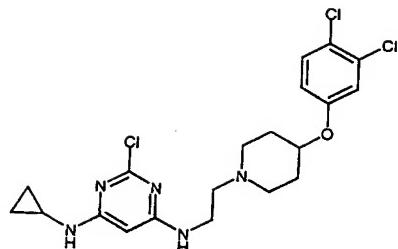
- 5 N~4-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2-,6-dimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 410 (M+1)

10 **Example 102**

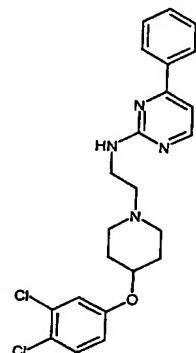
- 2-Chloro-N~4~-cyclopropyl-N~6~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-pyrimidinediamine



MS: APCI(+ve) 456 (M+1)

Example 103

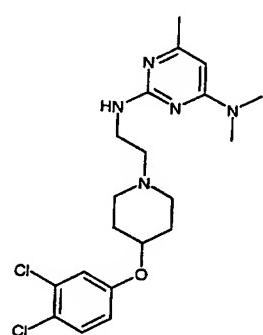
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenyl-2-pyrimidinamine



MS: APCI(+ve) 443 (M+1)

Example 104

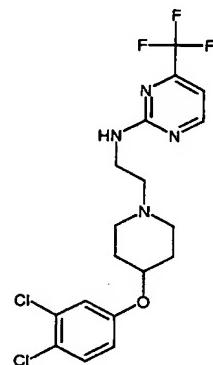
- 10 N~2~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 424 (M+1)

Example 105

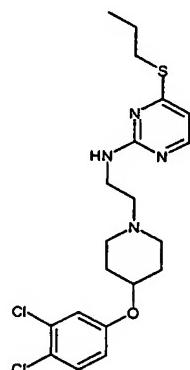
- 5 **N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-(trifluoromethyl)-2-pyrimidinamine**



MS: APCI(+ve) 435 (M+1)

Example 106

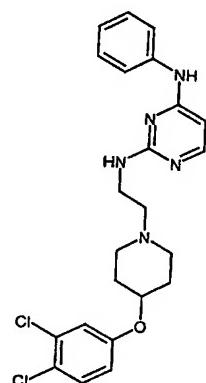
- 10 **N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4-(propylsulfanyl)-2-pyrimidinamine**



MS: APCI(+ve) 441 (M+1)

Example 107

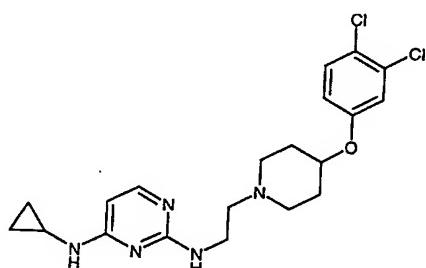
N-2-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-4-phenyl-2,4-pyrimidinediamine



5 MS: APCI(+ve) 458 (M+1)

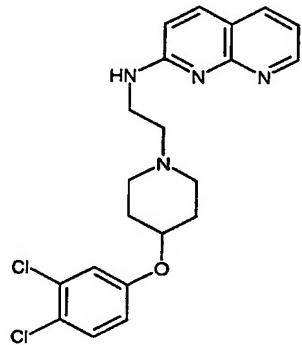
Example 108

N-4-Cyclopropyl-N-2-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine



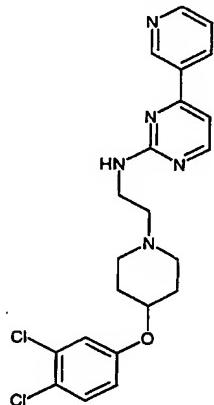
10

MS: APCI(+ve) 422 (M+1)

Example 109**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}[1,8]naphthyridin-2-amine**

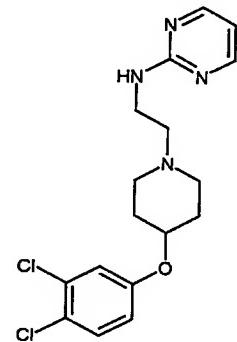
MS: APCI(+ve) 417 (M+1)

5

Example 110**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-pyridinyl)-2-pyrimidinamine**

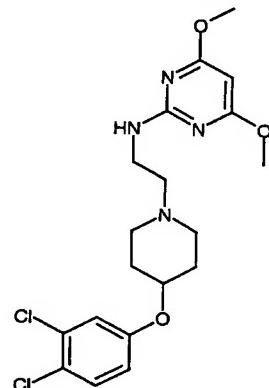
MS: APCI(+ve) 444 (M+1)

10

Example 111**N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-pyrimidinamine**

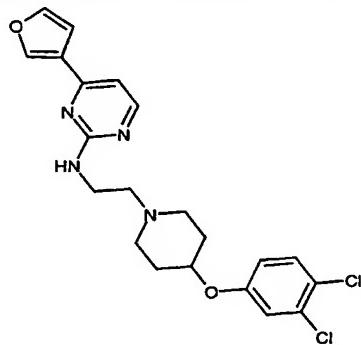
MS: APCI(+ve) 367 (M+1)

5

Example 112**N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-4,6-dimethoxy-2-pyrimidinamine**

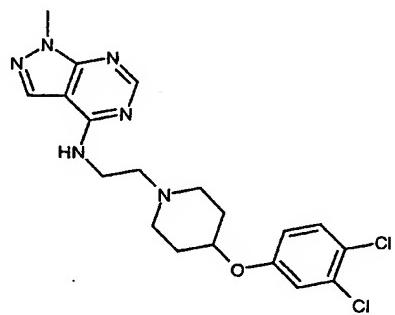
MS: APCI(+ve) 427 (M+1)

10

Example 113**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-furyl)-2-pyrimidinamine**

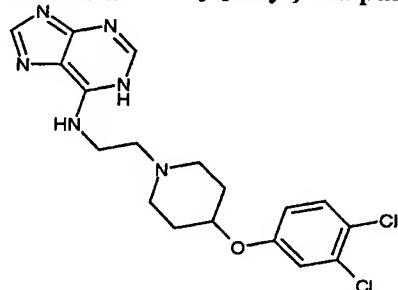
MS: APCI(+ve) 433 (M+1)

5

Example 114**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine**

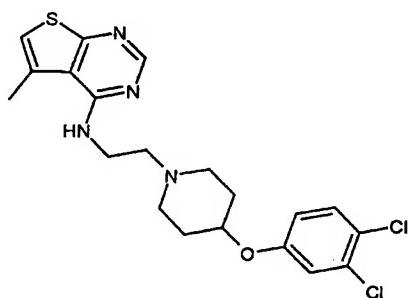
10

MS: APCI(+ve) 421 (M+1)

Example 115**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-purin-6-amine**

MS: APCI(+ve) 407 (M+1)

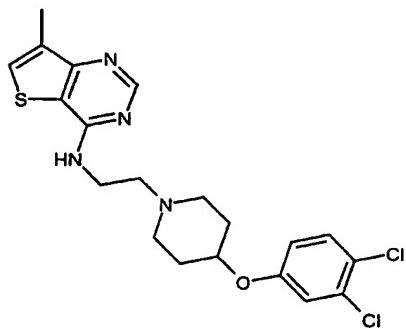
5

Example 116**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methylthieno[2,3-d]pyrimidin-4-amine**

10 MS: APCI(+ve) 437 (M+1)

Example 117

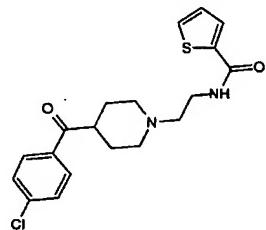
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-7-methylthieno[3,2-d]pyrimidin-4-amine



5 MS: APCI(+ve) 437 (M+1)

Example 118

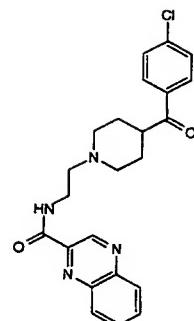
N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-2-thiophenecarboxamide



10 MS: APC1 (+ve) BP 377

Example 119

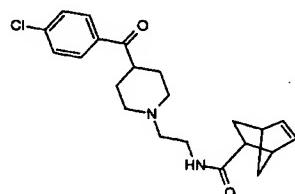
N-[2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl]-2-quinoxalinecarboxamide



MS: APC1 (+ve) BP 423

Example 120

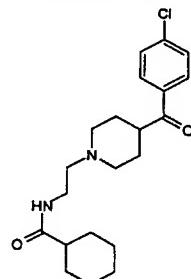
- 5 **N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide**



MS: APC1 (+ve) BP 387

10 **Example 121**

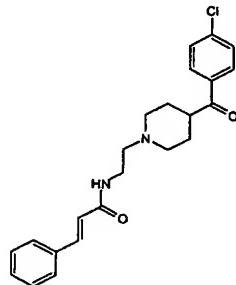
- N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}cyclohexanecarboxamide**



MS: APC1 (+ve) BP 377

Example 122

(E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide

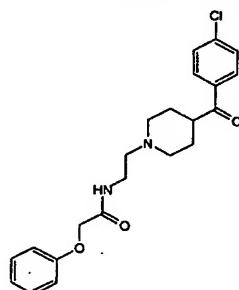


MS: APC1 (+ve) BP 397

5

Example 123

N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-phenoxyacetamide

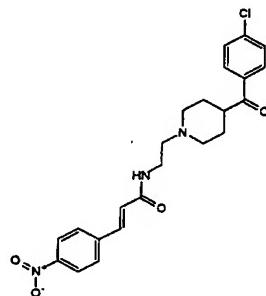


MS: APC1 (+ve) BP 401

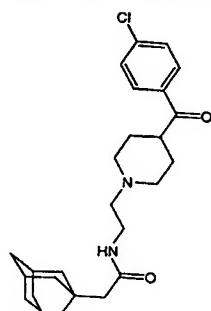
10

Example 124

(E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(4-nitrophenyl)-2-propenamide



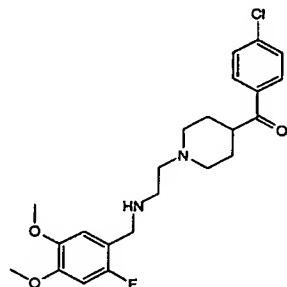
MS: APC1 (+ve) BP 442

Example 125**2-(1-Adamantyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}acetamide**

5

MS: APC1 (+ve) BP 443

The compounds of following Examples 126 to 168 were prepared by methods analogous to
10 the method of Example 30.

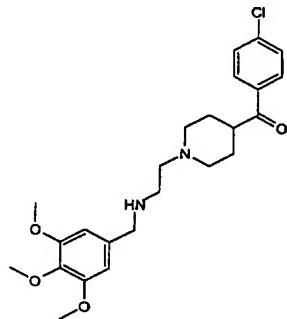
Example 126**(4-Chlorophenyl)(1-{2-[(2-fluoro-4,5-dimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone**

15

MS: APC1 (+ve) BP 435

Example 127

(4-Chlorophenyl)(1-{2-[{(3,4,5-trimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone

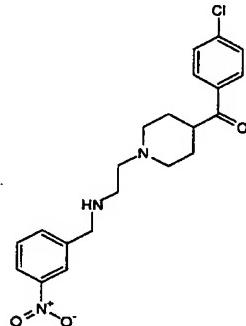


MS: APC1 (+ve) BP 447

5

Example 128

(4-Chlorophenyl)(1-{2-[{(3-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone

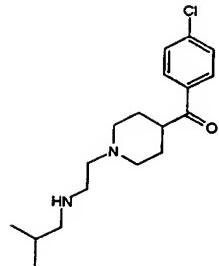


MS: APC1 (+ve) BP 402

10

Example 129

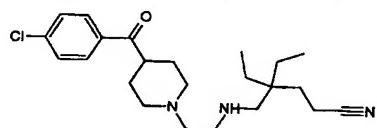
(4-Chlorophenyl){1-[2-(isobutylamino)ethyl]-4-piperidinyl}methanone



MS: APC1 (+ve) BP 323

Example 130

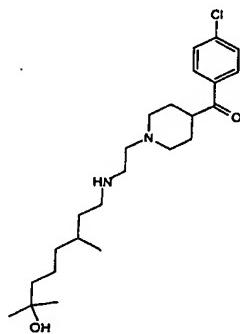
- 5 **4-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-4-ethylhexanenitrile**



MS: APC1 (+ve) BP 404

Example 131

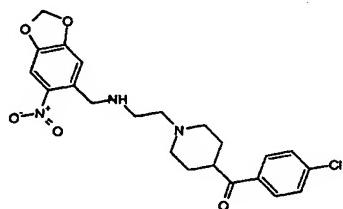
- 10 **(4-Chlorophenyl)(1-{2-[(7-hydroxy-3,7-dimethyloctyl)amino]ethyl}-4-piperidinyl)methanone**



MS: APC1 (+ve) BP 423

- 15 **Example 132**

(4-Chlorophenyl)[1-(2-{{(6-nitro-1,3-benzodioxol-5-yl)methyl}amino}ethyl)-4-piperidinyl]methanone

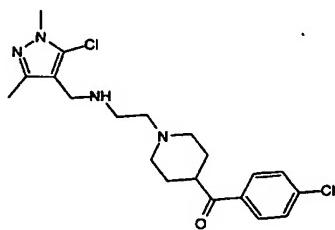


MS: APC1 (+ve) BP 446

5

Example 133

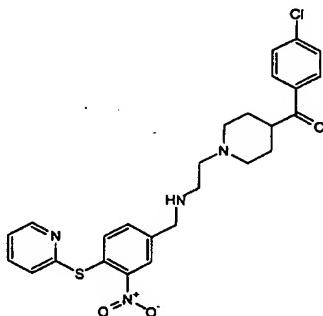
[1-(2-{{(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl}amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone



10 MS: APC1 (+ve) BP 409

Example 134

(4-Chlorophenyl)[1-(2-{{[3-nitro-4-(2-pyridinylsulfonyl)benzyl}amino}ethyl)-4-piperidinyl]methanone

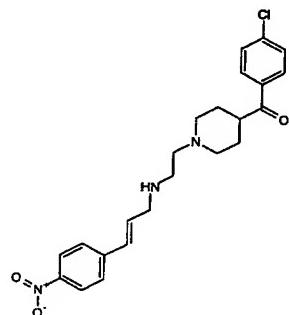


15

MS: APC1 (+ve) BP 511

Example 135

(4-Chlorophenyl)[1-(2-{{[(E)-3-(4-nitrophenyl)-2-propenyl]amino}ethyl}-4-piperidinyl]methanone



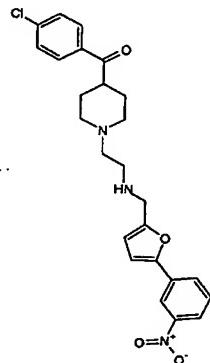
5

MS: APC1 (+ve) BP 428

Example 136

(4-Chlorophenyl){1-[2-{{[5-(3-nitrophenyl)-2-furyl]methyl}amino}ethyl]-4-piperidinyl}methanone

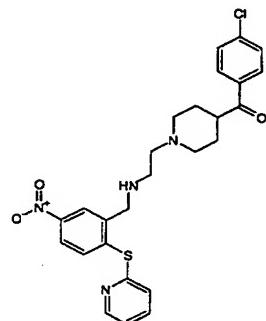
10



MS: APC1 (+ve) BP 468

Example 137

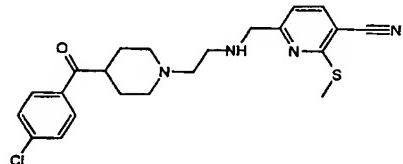
(4-Chlorophenyl)[1-(2-{{[5-nitro-2-(2-pyridinylsulfanyl)benzyl]amino}ethyl}-4-piperidinyl]methanone



5 MS: APC1 (+ve) BP 511

Example 138

6-[({2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-2-(methylsulfanyl)nicotinonitrile

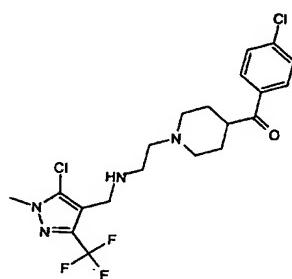


10

MS: APC1 (+ve) BP 429

Example 139

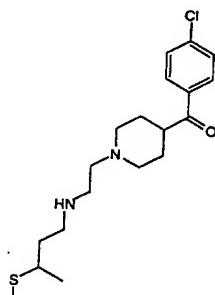
{1-[2-(2-{[5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)ethyl]-4-piperidinyl}(4-chlorophenyl)methanone



5 MS: APC1 (+ve) BP 463

Example 140

(4-Chlorophenyl)[1-(2-{[3-(methylsulfanyl)butyl]amino}ethyl)-4-piperidinyl]methanone

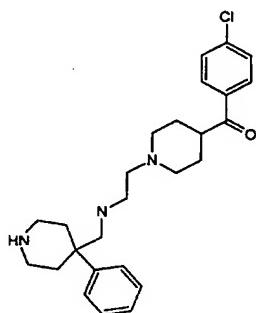


10

MS: APC1 (+ve) BP 369

Example 141

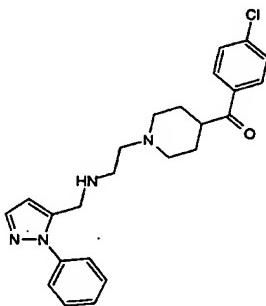
(4-Chlorophenyl)[1-(2-{{[(4-phenyl-4-piperidinyl)methyl]amino}ethyl}-4-piperidinyl]methanone



5 MS: APC1 (+ve) BP 440

Example 142

(4-Chlorophenyl)[1-(2-{{[(1-phenyl-1H-pyrazol-5-yl)methyl]amino}ethyl}-4-piperidinyl]methanone

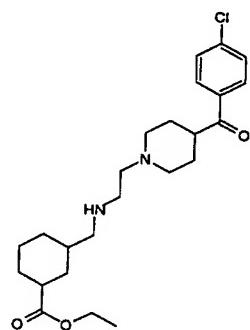


10

MS: APC1 (+ve) BP 423

Example 143

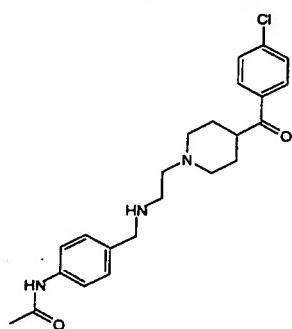
Ethyl 3-[({2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}-amino)methyl]cyclohexanecarboxylate



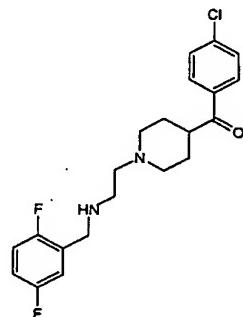
5 MS: APC1 (+ve) BP 435

Example 144

N-{4-[({2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]phenyl}acetamide

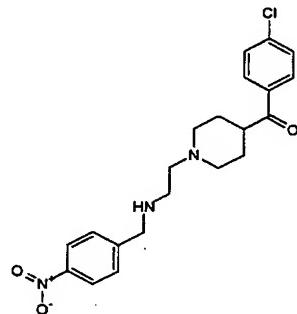


10 MS: APC1 (+ve) BP 414

Example 145**(4-Chlorophenyl)(1-{2-[(2,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone**

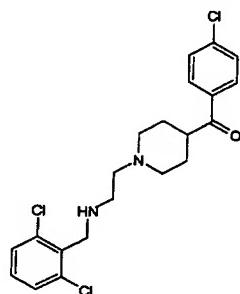
MS: APC1 (+ve) BP 393

5

Example 146**(4-Chlorophenyl)(1-{2-[(4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone**

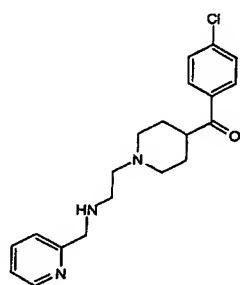
MS: APC1 (+ve) BP 402

10

Example 147**(4-Chlorophenyl)(1-{2-[(2,6-dichlorobenzyl)amino]ethyl}-4-piperidinyl)methanone**

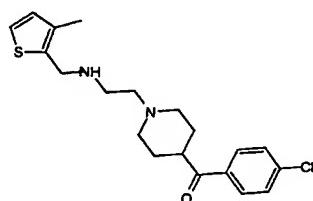
MS: APC1 (+ve) BP 425

5

Example 148**(4-Chlorophenyl)(1-{2-[(2-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone**

MS: APC1 (+ve) BP 358

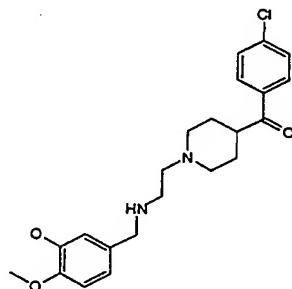
10

Example 149**(4-Chlorophenyl)[1-(2-{[(3-methyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone**

15 MS: APC1 (+ve) BP 377

Example 150

(4-Chlorophenyl)(1-{2-[{(3-hydroxy-4-methoxybenzyl)amino]ethyl}-4-piperidinyl)methanone

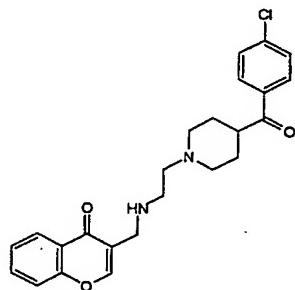


5

MS: APC1 (+ve) BP 403

Example 151

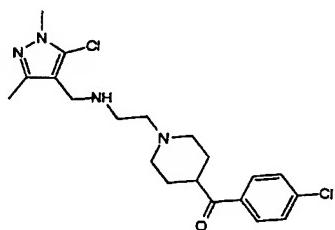
3-[{(2-[{4-(4-Chlorobenzoyl)-1-piperidinyl}ethyl]amino)methyl]-4H-chromen-4-one



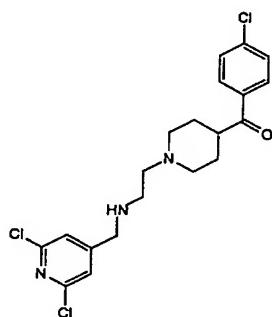
10

MS: APC1 (+ve) BP 425

100

Example 152**[1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone**

5 MS: APC1 (+ve) BP 409

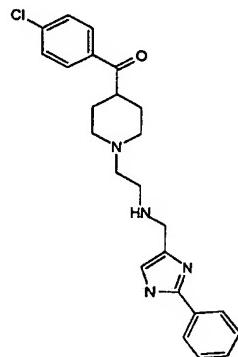
Example 153**(4-Chlorophenyl)[1-(2-{[(2,6-dichloro-4-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone**

10

MS: APC1 (+ve) BP 428

Example 154

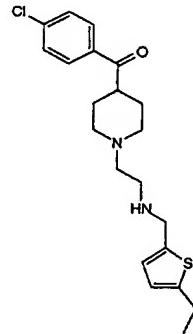
(4-Chlorophenyl)[1-(2-{{(2-phenyl-1H-imidazol-4-yl)methyl}amino}ethyl)-4-piperidinyl]methanone



MS: APC1 (+ve) BP 423

Example 155

(4-Chlorophenyl)[1-(2-{{(5-ethyl-2-thienyl)methyl}amino}ethyl)-4-piperidinyl]methanone

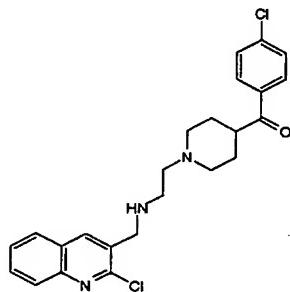


10

MS: APC1 (+ve) BP 391

Example 156

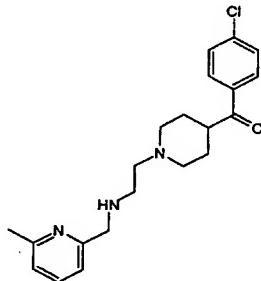
(4-Chlorophenyl)[1-(2-{{(2-chloro-3-quinolinyl)methyl}amino}ethyl)-4-piperidinyl]methanone



5 MS: APC1 (+ve) BP 442

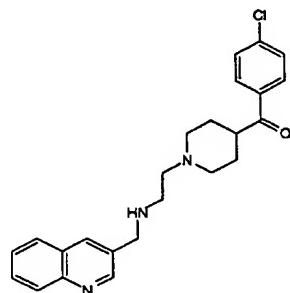
Example 157

(4-Chlorophenyl)[1-(2-{{(6-methyl-2-pyridinyl)methyl}amino}ethyl)-4-piperidinyl]methanone



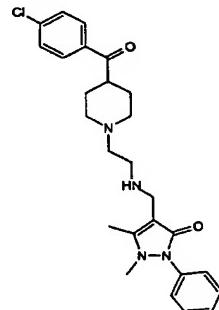
10

MS: APC1 (+ve) BP 372

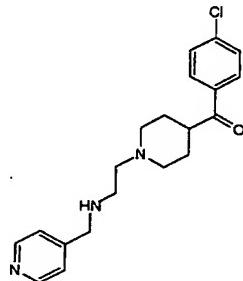
Example 158**(4-Chlorophenyl)(1-{2-[(3-quinolinylmethyl)amino]ethyl}-4-piperidinyl)methanone**

MS: APC1 (+ve) BP 408

5

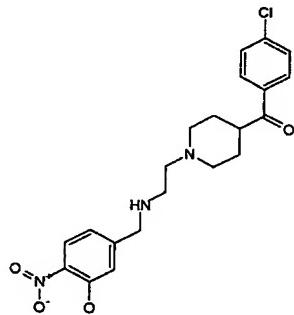
Example 159**4-[({2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one**

10 MS: APC1 (+ve) BP 467

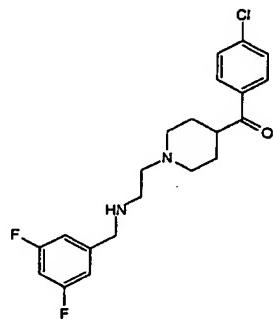
Example 160**(4-Chlorophenyl)(1-{2-[(4-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone**

MS: APC1 (+ve) BP 358

5

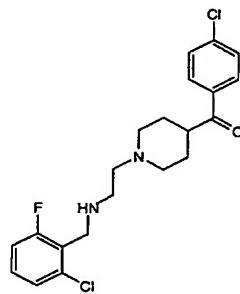
Example 161**(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone**

10 MS: APC1 (+ve) BP 418

Example 162**(4-Chlorophenyl)(1-{2-[(3,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone**

MS: APC1 (+ve) BP 393

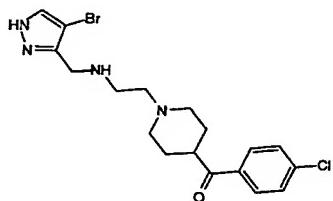
5

Example 163**(1-{2-[(2-Chloro-6-fluorobenzyl)amino]ethyl}-4-piperidinyl)(4-chlorophenyl)methanone**

10 MS: APC1 (+ve) BP 409

Example 164

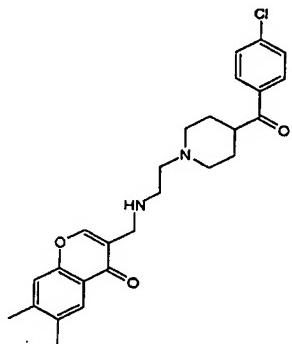
[1-(2-{{[4-Bromo-1H-pyrazol-3-yl]methyl}amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone



5 MS: APC1 (+ve) BP 427

Example 165

3-[({2-[4-Chlorobenzoyl]-1-piperidinyl}ethyl)amino)methyl]-6,7-dimethyl-4H-chromen-4-one

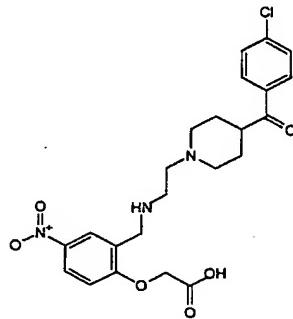


10

MS: APC1 (+ve) BP 453

Example 166

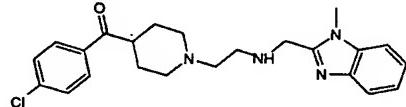
2-{2-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}amino)methyl]-4-nitrophenoxy}acetic acid



5 MS: APC1 (+ve) BP 476

Example 167

(4-Chlorophenyl)[1-(2-[(1-methyl-1H-benzimidazol-2-yl)methyl]amino)ethyl]-4-piperidinyl]methanone



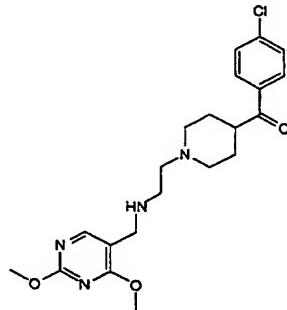
10

MS: APC1 (+ve) BP 411

Example 168

(4-Chlorophenyl)[1-(2-[(2,4-dimethoxy-5-pyrimidinyl)methyl]amino)ethyl]-4-piperidinyl]methanone

15



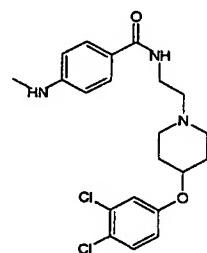
MS: APC1 (+ve) BP 419

The compounds of following Examples 169 to 209 were prepared by methods analogous to the method of Example 2.

5

Example 169

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylamino)benzamide

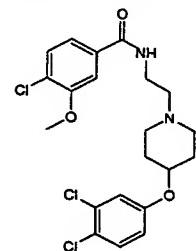


MS: APC1 (+ve) BP 422

10

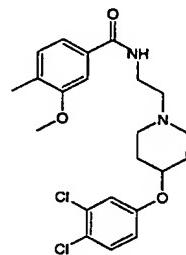
Example 170

4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide



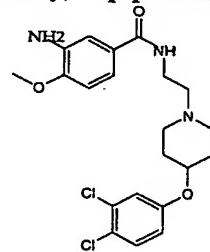
MS: APC1 (+ve) BP 459

15

Example 171**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-4-methylbenzamide**

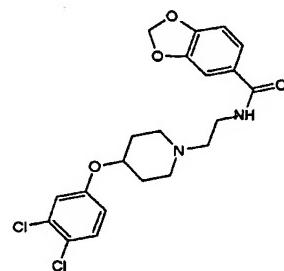
MS: APC1 (+ve) BP 437

5

Example 172**3-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide**

MS: APC1 (+ve) BP 438

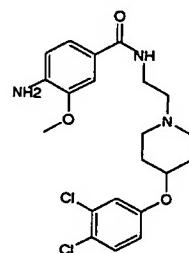
10

Example 173**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzodioxole-5-carboxamide**

MS: APC1 (+ve) BP 437

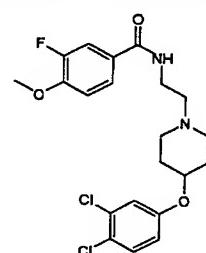
15

110

Example 174**4-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide**

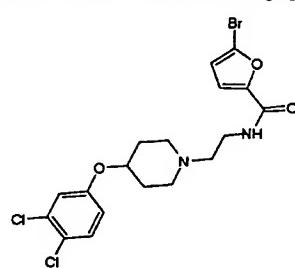
MS: APC1 (+ve) BP 438

5

Example 175**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluoro-4-methoxybenzamide**

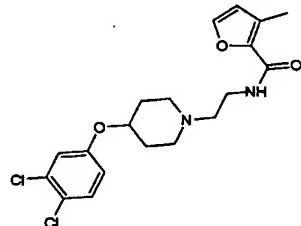
MS: APC1 (+ve) BP 441

10

Example 176**5-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide**

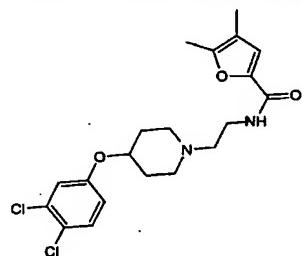
MS: APC1 (+ve) BP 463

15

Example 177**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methyl-2-furamide**

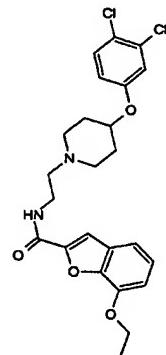
MS: APC1 (+ve) BP 397

5

Example 178**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,5-dimethyl-2-furamide**

MS: APC1 (+ve) BP 411

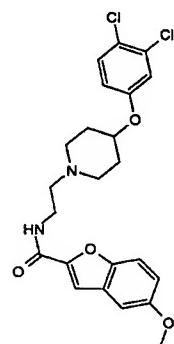
10

Example 179**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-ethoxy-1-benzofuran-2-carboxamide**

MS: APC1 (+ve) BP 477

Example 180

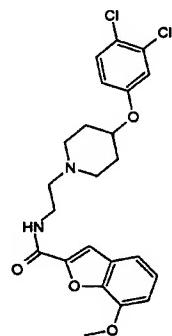
- 5 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-1-benzofuran-2-carboxamide**



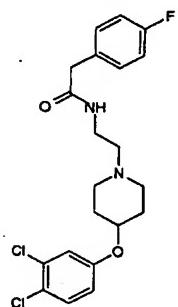
MS: APC1 (+ve) BP 463

Example 181

- 10 **N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methoxy-1-benzofuran-2-carboxamide**

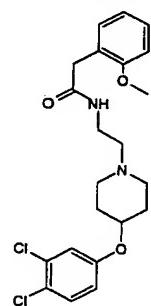


MS: APC1 (+ve) BP463

Example 182**N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-fluorophenyl)acetamide**

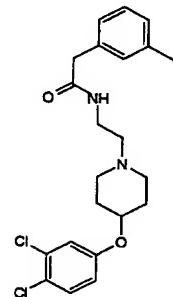
MS: APC1 (+ve) BP 425

5

Example 183**N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(2-methoxyphenyl)acetamide**

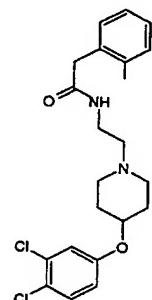
MS: APC1 (+ve) BP 437

10

Example 184**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methylphenyl)acetamide**

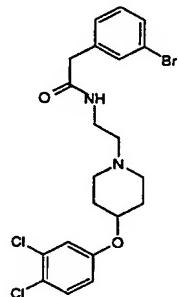
MS: APC1 (+ve) BP421

5

Example 185**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methylphenyl)acetamide**

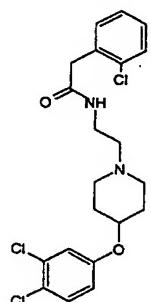
MS: APC1 (+ve) BP 421

10

Example 186**2-(3-Bromophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

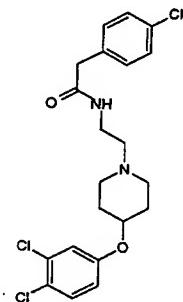
MS: APC1 (+ve) BP 487

5

Example 187**2-(2-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

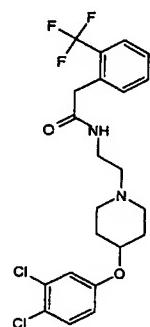
MS: APC1 (+ve) BP 441

10

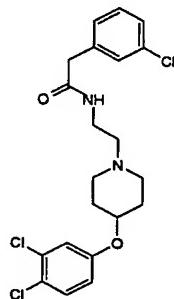
Example 188**2-(4-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

MS: APC1 (+ve) BP 443

5

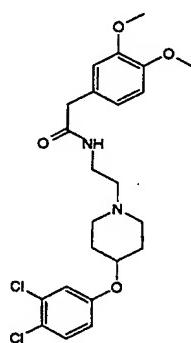
Example 189**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(trifluoromethyl)phenyl]acetamide**

10 MS: APC1 (+ve) BP 475

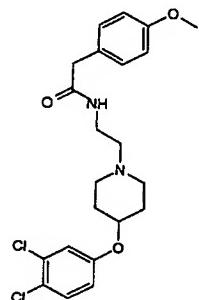
Example 190**2-(3-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide**

MS: APC1 (+ve) BP441

5

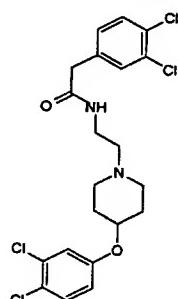
Example 191**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dimethoxyphenyl)acetamide**

10 MS: APC1 (+ve) BP467

Example 192**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methoxyphenyl)acetamide**

MS: APC1 (+ve) BP 437

5

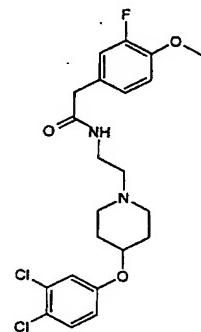
Example 193**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dichlorophenyl)acetamide**

MS: APC1 (+ve) BP 477

10

Example 194

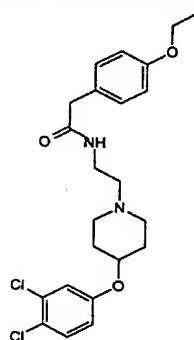
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(3-fluoro-4-methoxyphenyl)acetamide



5 MS: APC1 (+ve) BP 455

Example 195

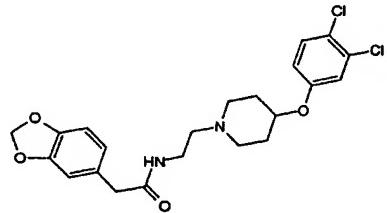
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-ethoxyphenyl)acetamide



10 MS: APC1 (+ve) BP 451

Example 196

2-(1,3-Benzodioxol-5-yl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide

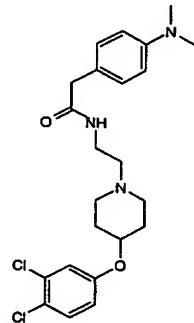


MS: APC1 (+ve) BP451

5

Example 197

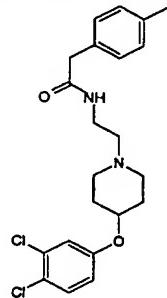
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[4-(dimethylamino)phenyl]acetamide



10 MS: APC1 (+ve) BP 450

Example 198

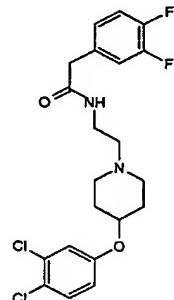
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methylphenyl)acetamide



MS: APC1 (+ve) BP 421

Example 199

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-difluorophenyl)acetamide

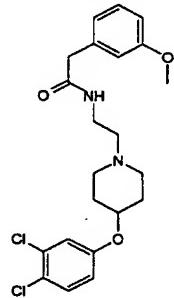


5

MS: APC1 (+ve) BP 443

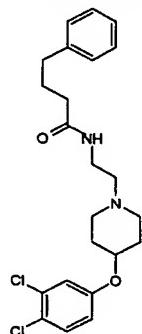
Example 200

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methoxyphenyl)acetamide



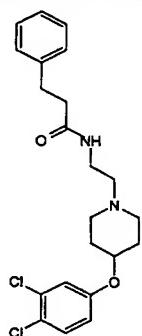
10

MS: APC1 (+ve) BP 437

Example 201**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenylbutanamide**

MS: APC1 (+ve) BP 435

5

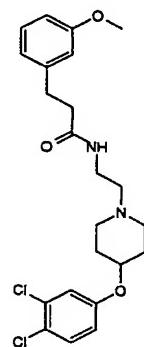
Example 202**N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenylpropanamide**

MS: APC1 (+ve) BP 421

10

Example 203

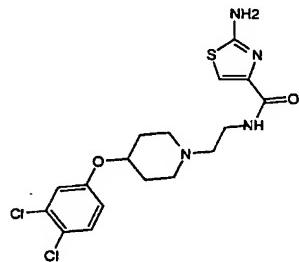
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-3-(3-methoxyphenyl)propanamide



5 MS: APC1 (+ve) BP 451

Example 204

2-Amino-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-1,3-thiazole-4-carboxamide

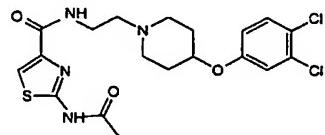


10

MS: APC1 (+ve) BP 416

Example 205

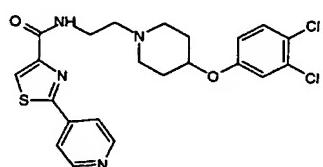
2-(Acetylamino)-N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-1,3-thiazole-4-carboxamide



MS: APC1 (+ve) BP 457

Example 206

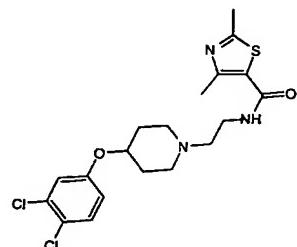
- 5 **N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-(4-pyridinyl)-1,3-thiazole-4-carboxamide**



MS: APC1 (+ve) BP 477

Example 207

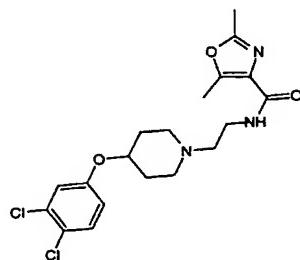
- 10 **N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide**



MS: APC1 (+ve) BP 428

Example 208

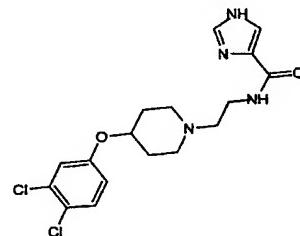
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide



5 MS: APC1 (+ve) BP 412

Example 209

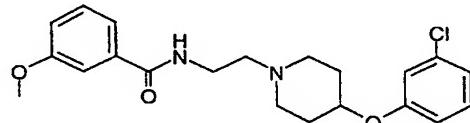
N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-1H-imidazole-4-carboxamide



10 MS: APC1 (+ve) BP 385.

Example 210

N-[2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl]-3-methoxybenzamide hydrochloride



(i) 2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethylamine trifluoroacetate

Prepared by the method of Example 1 steps (i) to (iv) using 3-chlorophenol to give the product as an oil (0.5 g) which was used directly in the next step without further purification.

5

(ii) N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride

The product of step (i) above (0.3g) was dissolved in dichloromethane (490ml), triethylamine (4 equiv) and 3-methoxybenzoyl chloride (1 equiv) were added. After 72 hours at room temperature, water was added, the organic phase separated, dried and concentrated to a gum. The product was dissolved in dichloromethane and treated with 1.0M ethereal hydrogen chloride solution to give the titled product as a solid (0.1 g).

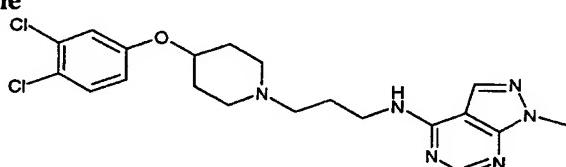
Melting point: 175-176 °C

15 MS: APCI(+ve): 389(M+H)

¹H NMR: δ(DMSO) 8.87 (t, 1H), 7.5 (m, 2H), 7.42 (m, 1H), 7.32 (m, 1H), 7.13 (m, 2H), 6.98 (m, 2H), 4.82 (m, 1/2H), 4.61 (m, 1/2H), 3.81 (s, 3H), 3.69 (m, 3H), 3.68 (m, 3H), 3.47 (m, 1H), 3.13-3.22 (m, 4H), 2.27 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.90 (m, 1H)

20 **Example 211**

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine



(i) 2-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-isoindole-1,3(2H)-dione

25 A solution of the product from Example 1 step (ii) (2.0g), 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione (1.61g) and triethylamine (2.5ml) in dichloromethane (40ml) was heated under reflux for 48h. The reaction mixture was partitioned between ethyl

acetate/water, the organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 4% methanol/dichloromethane. Yield 0.839g

MS: APCI(+ve) 433 (M+1)

5

(ii) 3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propylamine, dihydrochloride salt

The product from step (i) (0.83g) and hydrazine hydrate (0.1ml) in ethanol was heated under reflux for 6h. The precipitate was filtered off and partitioned between 2M hydrochloric acid and dichloromethane, the solid was filtered off and the aqueous layer basified with aqueous potassium hydroxide solution and extracted with dichloromethane. The organic layer was dried, evaporated under reduced pressure and the dihydrochloride salt formed using ethereal hydrogen chloride. Yield 0.28g

15 ^1H NMR: δ (DMSO-d₆) 11.11(br s, 1H), 8.13(br s, 3H), 7.56 (d, 1H), 7.37(s, 1H), 7.10-7.06(br m, 1H), 4.84(br s, 0.5H), 4.65(br s, 0.5H), 3.60-2.90(m, 8H), 2.24-2.01(m, 6H).

(iii) N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine

20 The product from step (ii) (0.08g), 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (0.054g) and diisopropylethylamine (0.082g) in 1-methyl-2-pyrrolidinone (2ml) was heated at 50°C for 3h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried and the solvent removed under reduced pressure. Purification was by chromatography eluting with 9% methanol/dichloromethane. Yield 0.052g

25 MS: APCI(+ve) 435 (M+1)

1 ^1H NMR: δ (DMSO-d₆) 8.25-8.22(m, 2H), 8.07(s, 1H), 7.49(d, 1H), 7.25(d, 1H), 6.97(dd, 1H), 4.46-4.42(m, 1H), 3.88(s, 3H), 3.49(q, 2H), 2.70-2.66(m, 2H), 2.40-2.36(m, 2H), 2.27-2.22(m, 2H), 1.92-1.88(m, 2H), 1.81-1.74(m, 2H), 1.62-1.59(m, 2H).

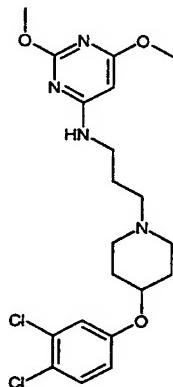
Melting point: 120-124°C

Examples 212-255

The product from Example 211 step (ii) (1.5mg), the appropriate activated halo aromatic (1.25 equivalents), diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrrolidinone (0.15ml) were heated at 100°C for 24h. The reaction mixture was evaporated to dryness
 5 and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 212

N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-2,6-dimethoxy-4-pyrimidinamine

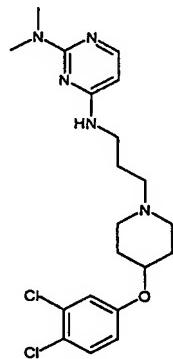


10

MS: APCI(+ve) 441 (M+1)

Example 213

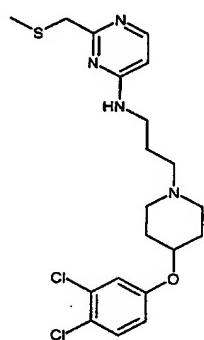
N~4~~{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,N~2~~dimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 424 (M+1)

Example 214

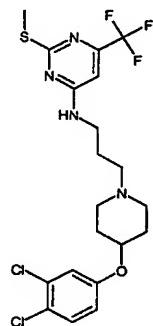
5 **N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine**



MS: APCI(+ve) 441 (M+1)

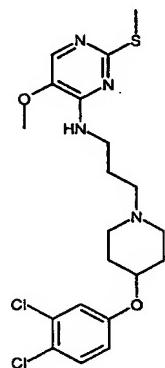
Example 215

10 **N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinamine**

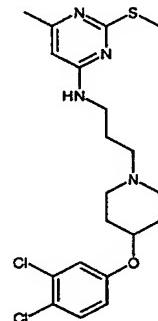


MS: APCI(+ve) 495 (M+1)

130

Example 216**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine**

5 MS: APCI(+ve) 457 (M+1)

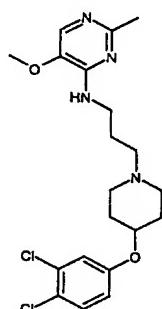
Example 217**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine**

10

MS: APCI(+ve) 441 (M+1)

Example 218

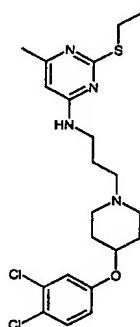
N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-5-methoxy-2-methyl-4-pyrimidinamine



5 MS: APCI(+ve) 425 (M+1)

Example 219

N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-2-(ethylsulfanyl)-6-methyl-4-pyrimidinamine

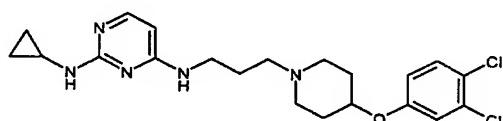


10

MS: APCI(+ve) 455 (M+1)

Example 220

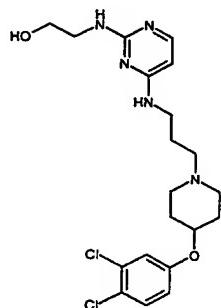
N~2~-Cyclopropyl-N~4~-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2,4-pyrimidinediamine



MS: APCI(+ve) 436 (M+1)

Example 221

2-{{4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl}amino}-1-ethanol

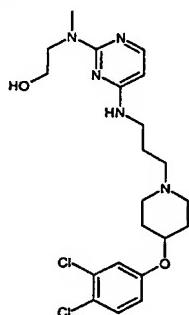


5

MS: APCI(+ve) 440 (M+1)

Example 222

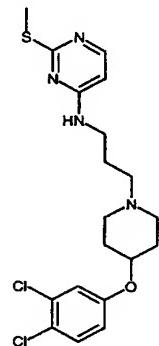
2-[[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl](methyl)amino]-1-ethanol



MS: APCI(+ve) 454 (M+1)

Example 223

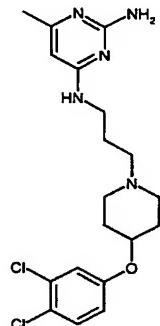
N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-2-(methylsulfanyl)-4-pyrimidinamine



5 MS: APCI(+ve) 427 (M+1)

Example 224

N-[4-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-6-methyl-2,4-pyrimidinediamine

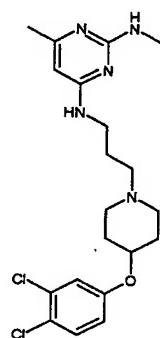


10

MS: APCI(+ve) 410 (M+1)

Example 225

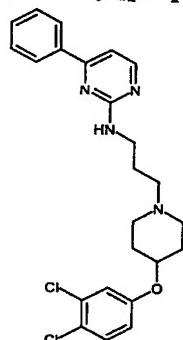
N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine



5 MS: APCI(+ve) 424 (M+1)

Example 226

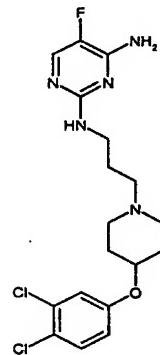
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-phenyl-2-pyrimidinamine



10 MS: APCI(+ve) 457 (M+1)

Example 227

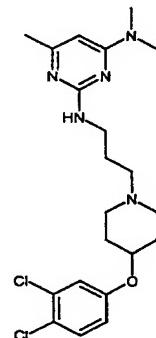
N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-fluoro-2,4-pyrimidinediamine



5 MS: APCI(+ve) 414 (M+1)

Example 228

N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine

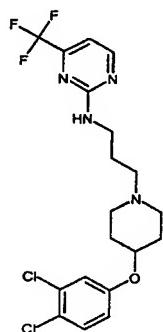


10

MS: APCI(+ve) 438 (M+1)

Example 229

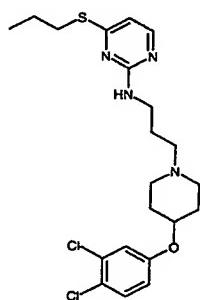
N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-4-(trifluoromethyl)-2-pyrimidinamine



5 MS: APCI(+ve) 449 (M+1)

Example 230

N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-4-(propylsulfanyl)-2-pyrimidinamine

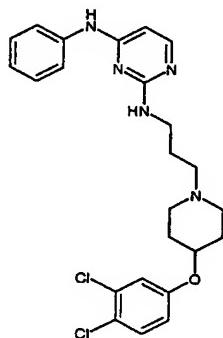


10

MS: APCI(+ve) 455 (M+1)

Example 231

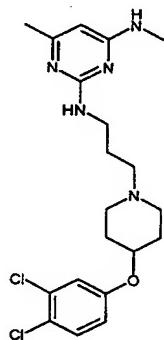
N~2~{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~-phenyl-2,4-pyrimidinediamine



5 MS: APCI(+ve) 472 (M+1)

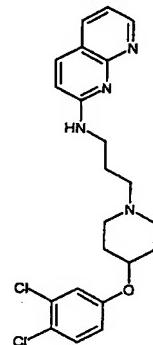
Example 232

N~2~{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,6-dimethyl-2,4-pyrimidinediamine



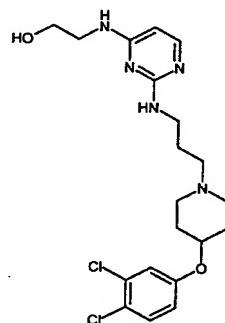
10

MS: APCI(+ve) 424 (M+1)

Example 233**N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl][1,8]naphthyridin-2-amine**

MS: APCI(+ve) 431 (M+1)

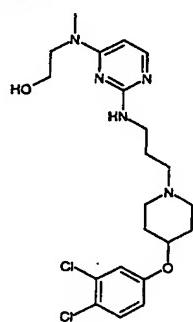
5

Example 234**2-{[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl]amino}-1-ethanol**

10 MS: APCI(+ve) 440 (M+1)

Example 235

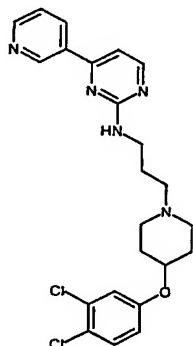
2-[[2-({3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl](methyl)amino]-1-ethanol



5 MS: APCI(+ve) 454 (M+1)

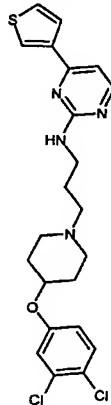
Example 236

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-pyridinyl)-2-pyrimidinamine



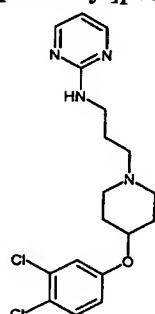
10

MS: APCI(+ve) 458 (M+1)

Example 237**N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-4-(3-thienyl)-2-pyrimidinamine**

MS: APCI(+ve) 463 (M+1)

5

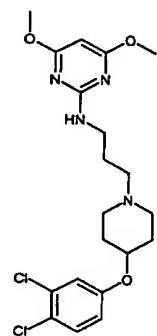
Example 238**N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-2-pyrimidinamine**

MS: APCI(+ve) 381 (M+1)

10

Example 239

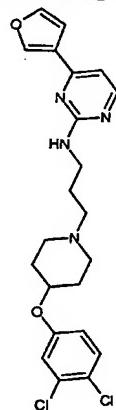
N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-4,6-dimethoxy-2-pyrimidinamine



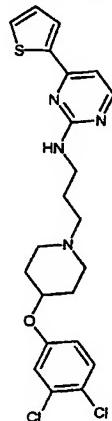
5 MS: APCI(+ve) 441 (M+1)

Example 240

N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-4-(3-furyl)-2-pyrimidinamine

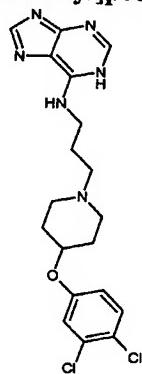


10 MS: APCI(+ve) 447 (M+1)

Example 241**N-[3-{4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(2-thienyl)-2-pyrimidinamine**

MS: APCI(+ve) 463 (M+1)

5

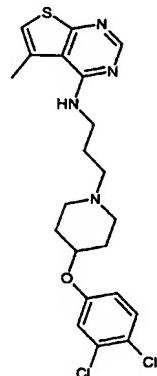
Example 242**N-[3-{4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-purin-6-amine**

MS: APCI(+ve) 421 (M+1)

10

Example 243

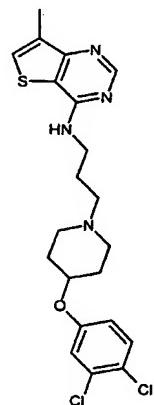
N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-5-methylthieno[2,3-d]pyrimidin-4-amine



5 MS: APCI(+ve) 451 (M+1)

Example 244

N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-7-methylthieno[3,2-d]pyrimidin-4-amine

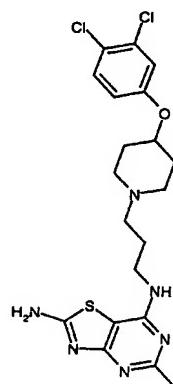


10

MS: APCI(+ve) 451 (M+1)

Example 245

N~7~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine

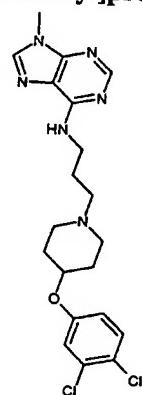


5

MS: APCI(+ve) 467 (M+1)

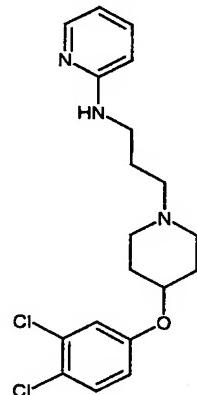
Example 246

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-9-methyl-9H-purin-6-amine



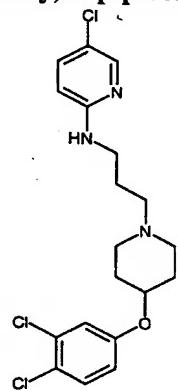
10

MS: APCI(+ve) 435 (M+1)

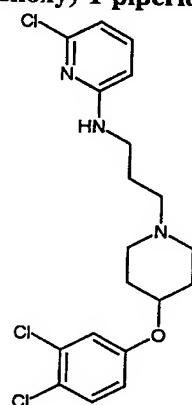
Example 247**N-[3-{4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine**

MS: APCI(+ve) 379 (M+1)

5

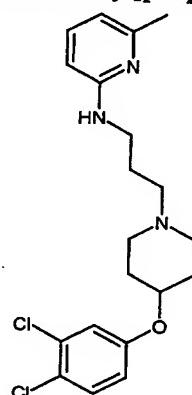
Example 248**5-Chloro-N-[3-{4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine**

MS: APCI(+ve) 414 (M+1)

Example 249**6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyridinamine**

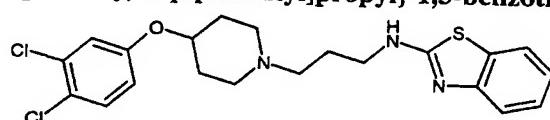
MS: APCI(+ve) 414 (M+1)

5

Example 250**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-pyridinamine**

MS: APCI(+ve) 494 (M+1)

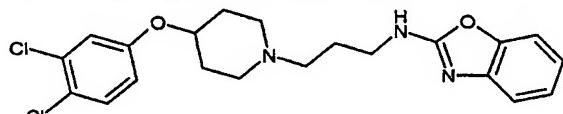
10

Example 251**N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzothiazol-2-amine**

MS: APCI(+ve) 436 (M+1)

Example 252

N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1,3-benzoxazol-2-amine

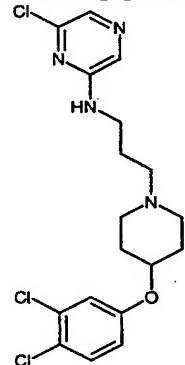


5

MS: APCI(+ve) 420 (M+1)

Example 253

6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrazinamine

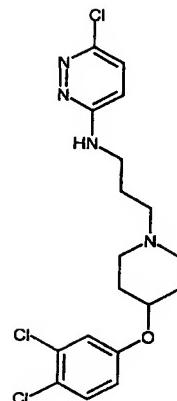


10

MS: APCI(+ve) 415 (M+1)

Example 254

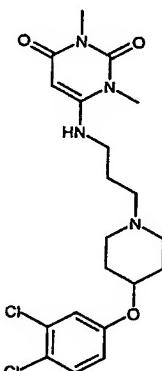
6-Chloro-N-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-3-pyridazinamine



MS: APCI(+ve) 417 (M+1)

Example 255

- 5 **6-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione**



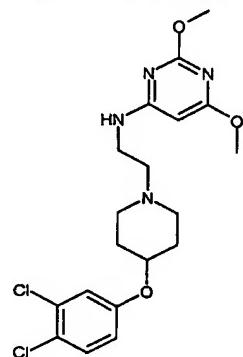
MS: APCI(+ve) 441 (M+1)

10 **Examples 256-292**

The product from Example 1 step (iv) (2.07mg), the appropriate activated halo aromatic (1.25 equivalents), diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrrolidinone (0.15ml) were heated at 100°C for 24h.. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 256

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2,6-dimethoxy-4-pyrimidinamine

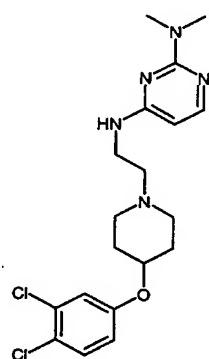


MS: APCI(+ve) 427 (M+1)

5

Example 257

N~4--{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine

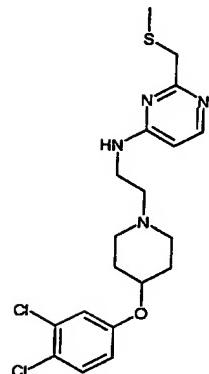


10 MS: APCI(+ve) 410 (M+1)

Example 258

N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-[(methylsulfanyl)methyl]-4-pyrimidinamine

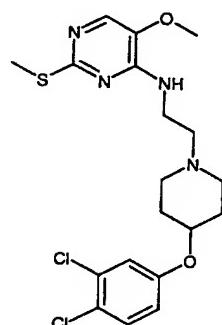
150



MS: APCI(+ve) 427 (M+1)

Example 259

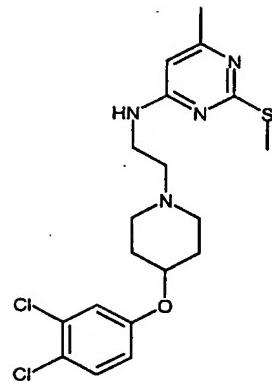
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine



MS: APCI(+ve) 443 (M+1)

10 **Example 260**

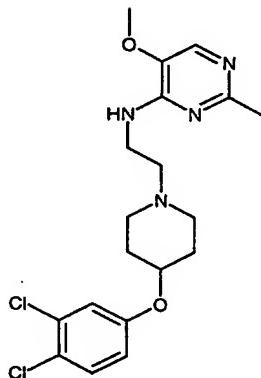
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine



MS: APCI(+ve) 427 (M+1)

5 **Example 261**

N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-2-methyl-4-pyrimidinamine

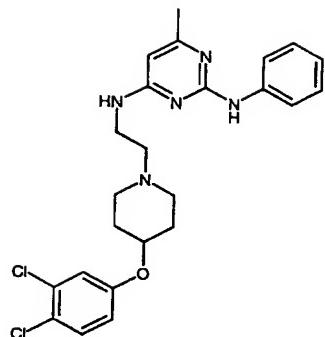


MS: APCI(+ve) 411 (M+1)

10

Example 262

N-4-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-N-2-phenyl-2,4-pyrimidinediamine



MS: APCI(+ve) 472 (M+1)

Pharmacological Analysis

5

Calcium flux $[Ca^{2+}]_i$ assay

a) Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5 \times 10^6 ml^{-1}$) and loaded with $5 \mu M$ FLUO-3/AM + Pluronic F127 2.2 $\mu l/ml$ (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, MgSO₄ 0.8mM, glucose 5.5mM, Na₂CO₃ 8.5mM, KCl 5mM, HEPES 20mM, CaCl₂ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5 \times 10^6 ml^{-1}$. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5 μM fibronectin for two hours) at 100ml/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200 μl ; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence ($\lambda_{Ex} = 490nm$ and $\lambda_{Em} = 520nm$) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

b) Human monocytes

Human monocytes were isolated from EDTA anticoagulated peripheral blood as previously described (Cunoosamy & Holbrook, *J. Leukocyte Biology*, 1998, S2, 13). Cells were resuspended ($5 \times 10^6 \text{ ml}^{-1}$) in LKS and loaded with $5 \mu\text{M}$ FLUO-3/AM + Pluronic F127 2.2 $\mu\text{l}/\text{ml}$ (Molecular Probes) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $0.5 \times 10^6 \text{ ml}^{-1}$. The cells were then transferred to 96 well FLIPr plates (Costar). To each well 100 μl of cells were added at a concentration of $0.5 \times 10^6 \text{ ml}^{-1}$. The plates were centrifuged (200g; 5 mins; room temperature) to allow the cells to adhere. After centrifugation the cells were washed twice with LKS (200 μl ; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of MIP-1 α and the transient increase in fluo-3 fluorescence ($\lambda_{\text{Ex}} = 490\text{nm}$ and $\lambda_{\text{Em}} = 520\text{nm}$) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of the Examples were found to be antagonists of the eotaxin mediated $[\text{Ca}^{2+}]_i$ in human eosinophils and/or antagonists of the MIP-1 α mediated $[\text{Ca}^{2+}]_i$ in human monocytes.

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10 \times 10^6 \text{ ml}^{-1}$ in RPMI containing 200 IU/ml penicillin, 200 $\mu\text{g}/\text{ml}$ streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis plate

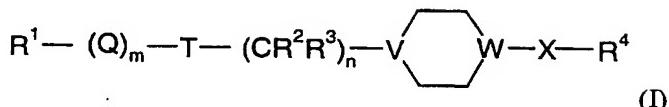
(ChemoTx, 3 μ m pore, Neuroprobe) was loaded by adding 28 μ l of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μ l of eosinophil suspension were added to the top of the filter. The 5 plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO₂ atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) 10 containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μ l of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the 15 supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated 20 human eosinophil chemotaxis.

CLAIMS

1. A compound of general formula



wherein:

R^1 represents a C_1 - C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio and C_1 - C_6 alkoxy carbonyl groups, or

10 R¹ represents a 3- to 10-membered saturated or unsaturated ring system which may comprise up to two ring carbon atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one or more substituents independently selected from halogen atoms, and cyano, nitro, hydroxyl, C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
15 C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -NR⁵R⁶, C₃-C₆ cycloalkylamino, C₁-C₆ alkylthio, C₁-C₆ alkylthio C₁-C₆ alkyl, C₁-C₆ alkylcarbonylamino, -C(O)NR⁷R⁸, sulphonamido, (di)C₁-C₆ alkylsulphonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and C(O)R⁹-substituted C₁-C₆ alkyl or C₁-C₆ alkoxy groups;

20 m is 0 or 1;

Q represents a group OCH_2 , $\text{C}_1\text{-C}_4$ alkylene or $\text{C}_2\text{-C}_4$ alkenylene:

T represents a group C(O)NH, or when m is 0, T may additionally represent a bond or a group NH, or when m is 1 and Q represents C₁-C₄ alkylene, T may additionally represent a group NH:

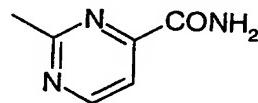
25 n is 1, 2, 3 or 4:

each R² independently represents a hydrogen atom or a C₁-C₄ alkyl group;

each R³ independently represents a hydrogen atom or a C₁-C₄ alkyl group;

V represents a nitrogen atom:

- W represents a nitrogen atom or a group CH;
- X represents an oxygen atom or a group C(O), CH(OH), NH or N(C₁-C₆ alkyl), provided that when W represents a nitrogen atom, then X represents C(O);
- R⁴ represents a phenyl group optionally substituted by one or more substituents
- 5 independently selected from halogen atoms, and amino, nitro, cyano, sulphonyl, sulphonamido, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy and C₁-C₆ alkylsulphonyl groups;
- R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₆ alkyl or hydroxyC₁-C₆ alkyl group, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring;
- 10 R⁷ and R⁸ each independently represent a hydrogen atom or a C₁-C₆ alkyl group; and R⁹ represents a hydroxyl or -NR⁷R⁸ group;
- with the provisos that
- (a) when m is 0, T is CONH, n is 2, 3 or 4 and each R² and R³ represents hydrogen, W is CH, X is C(O) or CH(OH) and R¹ represents a substituted 3- to 10-membered unsaturated ring system, then the one or more substituents in the ring system do not include hydroxyl, halogen, C₁-C₆ alkoxy or C₁-C₆ haloalkoxy, and
- 15 (b) when W is N, X is C(O), R⁴ represents 3-trifluoromethylphenyl, m is 0 and T is a bond, then R¹ and (CR²R³)_n taken together do not represent a C₁-C₆ alkyl group, and
- (c) when W is CH, X is O, n is 2 or 3 and each R² and R³ represents hydrogen, m is 0 and T is NH, then R¹ does not represent a group
- 20



; or a pharmaceutically acceptable salt or solvate thereof.

25

2. A compound according to claim 1, wherein R¹ represents a C₁-C₁₀ alkyl group optionally substituted by one or two substituents independently selected from cyano, hydroxyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio and C₁-C₄ alcoxycarbonyl groups, or

R¹ represents a 3- to 10-membered saturated or unsaturated ring system comprising up to two ring carbon atoms that form carbonyl groups and comprising up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulfur, the ring system being optionally substituted by one, two or three substituents independently selected from halogen atoms,
5 and cyano, nitro, hydroxyl, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, C₁-C₃ haloalkyl, C₁-C₃ haloalkoxy, -NR⁵R⁶, C₃-C₆ cycloalkylamino, C₁-C₄ alkylthio, C₁-C₄ alkylthioC₁-C₄ alkyl,
10 C₁-C₄ alkylcarbonylamino, -C(O)NR⁷R⁸, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, and C(O)R⁹-substituted C₁-C₄ alkyl or C₁-C₄ alkoxy groups.

3. A compound according to claim 1 or claim 2, wherein m is 1 and Q represents a group OCH₂, C₁-C₃ alkylene or C₂-C₃ alkenylene.

15 4. A compound according to any one of claims 1 to 3, wherein T represents a group C(O)NH.

5. A compound according to any one of the preceding claims, wherein n is 2 or 3.

20 6. A compound according to any one of the preceding claims, wherein V represents a nitrogen atom and W represents a group CH.

7. A compound according to any one of the preceding claims, wherein X represents an oxygen atom or a group C(O) or NH.

25 8. A compound according to any one of the preceding claims, wherein R⁴ represents a phenyl group optionally substituted by one or two halogen atoms.

9. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof,
30 according to claim 1 being selected from:

- 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-(dimethylamino)-2-oxoethoxy]benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-ethoxybenzamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-isopropoxybenzamide,
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-ethoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethoxy)benzamide
10 hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide hydrochloride,
3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide hydrochloride,
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide hydrochloride,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-hydroxybenzamide hydrochloride,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-[2-(methylamino)-2-
oxoethoxy]benzamide hydrochloride,
20 2-[3-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]ethyl}-2,4-dioxo-3,4-dihydro-1(2H)-
quinazolinyl]-N,N-dimethylacetamide hydrochloride,
N-{2-[4-(3,4-Dichlorobenzoyl)-1-piperazinyl]ethyl}-3-methoxybenzamide hydrochloride,
3,4-Dichloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}benzamide,
4-Chloro-N-{2-[4-(3,4-dichlorobenzoyl)-1-piperazinyl]ethyl}-2-[2-(dimethylamino)-2-
25 oxoethoxy]benzamide hydrochloride,
N~7~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methyl[1,3]thiazolo[4,5-
d]pyrimidine-2,7-diamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-9-methyl-9H-purin-6-amine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzothiazol-2-amine,
30 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzoxazol-2-amine,

- 6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrazinamine,
6-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-pyridazinamine,
6-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-1,3-dimethyl-2,4(1H,3H)-
pyrimidinedione,
- 5 N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-4-methyl-
benzamide, hydrochloride salt,
- N-{1-[4-(3,4-Dichlorophenoxy)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-methoxy-
benzamide, hydrochloride salt,
- N-{2-[4-(3,4-Dichloroanilino)-1-piperidinyl]ethyl}-3-methoxybenzamide dihydrochloride,
- 10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N-(3-methoxybenzyl)amine
dihydrochloride,
- 3-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methoxy-2,4(1H,3H)-
quinazolinenedione,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluorobenzamide,
- 15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,
- 20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-nitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methylbenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-dinitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-iodobenzamide,
- 25 4-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
4-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methylbenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-nitrobenzamide,
3-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
- 30 3,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-fluorobenzamide,
2,4-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methylbenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-iodobenzamide,
5 4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-nitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-5-(trifluoromethyl)benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(trifluoromethoxy)benzamide,
10 3,5-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)benzamide,
3-Cyano-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
2-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,
15 3-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
2-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3,5-difluorobenzamide,
2,3-Dichloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-naphthamide,
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-fluoro-6-(trifluoromethyl)benzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-difluorobenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,
Methyl 4-({2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}amino)-4-oxobutanoate,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclobutanecarboxamide,
30 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-methoxyacetamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclohexanecarboxamide,
(E)-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,
2-Chloro-N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}nicotinamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenylacetamide,
5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}cyclopentanecarboxamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-phenoxyacetamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(trifluoromethyl)benzamide,
4-(tert-Butyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}benzamide,
10 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methylbenzamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-nitrobenzamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-methylbenzamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-4-methyl-3-nitrobenzamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-cyanobenzamide,
15 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-furamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-nitrobenzamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-naphthamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(methylsulfanyl)nicotinamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1,3-
20 thiazole-4-carboxamide,
N~2~-Cyclopropyl-N~4~-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-
pyrimidinediamine,
2-{{4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-pyrimidinyl}amino}-1-
ethanol,
25 2-{{4-({2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}amino)-2-
pyrimidinyl}(methyl)amino}-1-ethanol,
N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~-phenyl-2,4-
pyrimidinediamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(methylsulfanyl)-4-pyrimidinamine,
30 N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-2,4-pyrimidinediamine,

- N~4~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,
- 2-Chloro-N~4~~cyclopropyl-N~6~~{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-pyrimidinediamine,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenyl-2-pyrimidinamine,
N~2~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~,N~4~,6-trimethyl-2,4-pyrimidinediamine,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(trifluoromethyl)-2-pyrimidinamine,
- 10 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(propylsulfanyl)-2-pyrimidinamine,
N~2~~{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~4~~phenyl-2,4-pyrimidinediamine,
- N~4~~Cyclopropyl-N~2~~{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-pyrimidinediamine,
- 15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}[1,8]naphthyridin-2-amine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-pyridinyl)-2-pyrimidinamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-pyrimidinamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,6-dimethoxy-2-pyrimidinamine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(3-furyl)-2-pyrimidinamine,
- 20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-purin-6-amine,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methylthieno[2,3-d]pyrimidin-4-amine,
- 25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methylthieno[3,2-d]pyrimidin-4-amine,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-thiophenecarboxamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-quinoxalinecarboxamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide,
- 30 N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}cyclohexanecarboxamide,

- (E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-phenyl-2-propenamide,
N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-2-phenoxyacetamide,
(E)-N-{2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl}-3-(4-nitrophenyl)-2-propenamide,
2-(1-Adamantyl)-N-{2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl}acetamide,
5 (4-Chlorophenyl)(1-{2-[(2-fluoro-4,5-dimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(3,4,5-trimethoxybenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(3-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl){1-[2-(isobutylamino)ethyl]-4-piperidinyl}methanone,
10 4-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-ethylhexanenitrile,
(4-Chlorophenyl)(1-{2-[(7-hydroxy-3,7-dimethyloctyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-[(6-nitro-1,3-benzodioxol-5-yl)methyl]amino)ethyl]-4-piperidinyl)methanone,
15 [1-(2-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino)ethyl]-4-piperidinyl](4-chlorophenyl)methanone;
(4-Chlorophenyl)[1-(2-[(3-nitro-4-(2-pyridinylsulfanyl)benzyl)amino]ethyl)-4-piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-[(E)-3-(4-nitrophenyl)-2-propenyl]amino)ethyl]-4-piperidinyl)methanone,
20 (4-Chlorophenyl)[1-(2-[(5-(3-nitrophenyl)-2-furyl)methyl]amino)ethyl]-4-piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-[(5-nitro-2-(2-pyridinylsulfanyl)benzyl)amino]ethyl)-4-piperidinyl)methanone,
25 6-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-2-(methylsulfanyl)nicotinonitrile,
{1-[2-([(5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methyl]amino)ethyl]-4-piperidinyl}(4-chlorophenyl)methanone,
(4-Chlorophenyl)[1-(2-[(3-(methylsulfanyl)butyl)amino]ethyl)-4-piperidinyl)methanone,

- (4-Chlorophenyl)[1-(2-{[(4-phenyl-4-piperidinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{[(1-phenyl-1H-pyrazol-5-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,
- 5 Ethyl 3-[{(2-[4-(4-chlorobenzoyl)-1-piperidinyl]ethyl)-amino)methyl]cyclohexanecarboxylate,
- N-{4-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]phenyl}acetamide,
- (4-Chlorophenyl)(1-{2-[(2,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
- (4-Chlorophenyl)(1-{2-[(4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
- 10 (4-Chlorophenyl)(1-{2-[(2,6-dichlorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
- (4-Chlorophenyl)(1-{2-[(2-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
- (4-Chlorophenyl)[1-(2-{[(3-methyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)(1-{2-[(3-hydroxy-4-methoxybenzyl)amino]ethyl}-4-
- 15 piperidinyl)methanone,
- 3-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4H-chromen-4-one,
- [1-(2-{[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,
- (4-Chlorophenyl)[1-(2-{[(2,6-dichloro-4-pyridinyl)methyl]amino}ethyl)-4-
- 20 piperidinyl)methanone,
- (4-Chlorophenyl)[1-(2-{[(2-phenyl-1H-imidazol-4-yl)methyl]amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{[(5-ethyl-2-thienyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{[(2-chloro-3-quinolinyl)methyl]amino}ethyl)-4-
- 25 piperidinyl]methanone,
- (4-Chlorophenyl)[1-(2-{[(6-methyl-2-pyridinyl)methyl]amino}ethyl)-4-piperidinyl]methanone,
- (4-Chlorophenyl)(1-{2-[(3-quinolinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
- 4-[{(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-1,5-dimethyl-2-phenyl-
- 30 1,2-dihydro-3H-pyrazol-3-one,

- (4-Chlorophenyl)(1-{2-[(4-pyridinylmethyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(3-hydroxy-4-nitrobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(4-Chlorophenyl)(1-{2-[(3,5-difluorobenzyl)amino]ethyl}-4-piperidinyl)methanone,
(1-{2-[(2-Chloro-6-fluorobenzyl)amino]ethyl}-4-piperidinyl)(4-chlorophenyl)methanone,
5 [1-(2-{[(4-Bromo-1H-pyrazol-3-yl)methyl]amino}ethyl)-4-piperidinyl](4-chlorophenyl)methanone,
3-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-6,7-dimethyl-4H-chromen-4-one,
2-{2-[(2-[4-(4-Chlorobenzoyl)-1-piperidinyl]ethyl)amino)methyl]-4-nitrophenoxy}acetic
10 acid,
(4-Chlorophenyl)[1-(2-{[(1-methyl-1H-benzimidazol-2-yl)methyl]amino}ethyl)-4-piperidinyl)methanone,
(4-Chlorophenyl)[1-(2-{[(2,4-dimethoxy-5-pyrimidinyl)methyl]amino}ethyl)-4-piperidinyl)methanone,
15 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-(methylamino)benzamide,
4-Chloro-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxy-4-methylbenzamide,
3-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-4-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-benzodioxole-5-carboxamide,
20 4-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-fluoro-4-methoxybenzamide,
5-Bromo-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-2-furamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-methyl-2-furamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4,5-dimethyl-2-furamide,
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-ethoxy-1-benzofuran-2-carboxamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-5-methoxy-1-benzofuran-2-carboxamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-7-methoxy-1-benzofuran-2-carboxamide,
30

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-fluorophenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methoxyphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methylphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(2-methylphenyl)acetamide,
5 2-(3-Bromophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,
2-(2-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,
2-(4-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[2-
(trifluoromethyl)phenyl]acetamide,
10 2-(3-Chlorophenyl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dimethoxyphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methoxyphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-dichlorophenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-fluoro-4-
15 methoxyphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-ethoxyphenyl)acetamide,
2-(1,3-Benzodioxol-5-yl)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-[4-
(dimethylamino)phenyl]acetamide,
20 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-methylphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3,4-difluorophenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(3-methoxyphenyl)acetamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-4-phenylbutanamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-phenylpropanamide,
25 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-3-(3-methoxyphenyl)propanamide,
2-Amino-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-carboxamide,
2-(Acetylamino)-N-{2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl}-1,3-thiazole-4-
carboxamide,
N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2-(4-pyridinyl)-1,3-thiazole-4-
30 carboxamide,

- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,4-dimethyl-1,3-thiazole-5-carboxamide,
- N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-2,5-dimethyl-1,3-oxazole-4-carboxamide,
- 5 N-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-1H-imidazole-4-carboxamide,
- N-{2-[4-(3,4-Chlorophenoxy)-1-piperidinyl]ethyl}-3-methoxybenzamide, hydrochloride salt,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- 10 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2,6-dimethoxy-4-pyrimidinamine,
- N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,N~2~-dimethyl-2,4-pyrimidinediamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,
- 15 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,
- 20 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-methoxy-2-methyl-4-pyrimidinamine,
- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(ethylsulfanyl)-6-methyl-4-pyrimidinamine,
- 25 N~2~-Cyclopropyl-N~4~-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl}-2,4-pyrimidinediamine,
- 2-{[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl]amino}-1-ethanol,
- 2-[[4-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-2-pyrimidinyl](methyl)amino]-1-ethanol,
- 30

- N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-(methylsulfanyl)-4-pyrimidinamine,
N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-6-methyl-2,4-pyrimidinediamine,
5 N~4~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~2~,6-dimethyl-2,4-pyrimidinediamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-phenyl-2-pyrimidinamine,
N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-5-fluoro-2,4-pyrimidinediamine,
N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,N~4~,6-trimethyl-2,4-
10 pyrimidinediamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(trifluoromethyl)-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(propylsulfanyl)-2-pyrimidinamine,
15 N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~-phenyl-2,4-pyrimidinediamine,
N~2~-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-N~4~,6-dimethyl-2,4-pyrimidinediamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}[1,8]naphthyridin-2-amine,
20 2-{[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl]amino}-1-ethanol,
2-[[2-({3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}amino)-4-pyrimidinyl](methyl)amino]-1-ethanol,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-pyridinyl)-2-pyrimidinamine,
25 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-thienyl)-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4,6-dimethoxy-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(3-furyl)-2-pyrimidinamine,
N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-4-(2-thienyl)-2-pyrimidinamine,
30 N-{3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl}-1H-purin-6-amine,

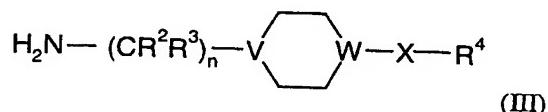
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-5-methylthieno[2,3-d]pyrimidin-4-amine,
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-7-methylthieno[3,2-d]pyrimidin-4-amine,
- 5 N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-5-methyl[1,3]thiazolo[4,5-d]pyrimidine-2,7-diamine,
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-9-methyl-9H-purin-6-amine,
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-2-pyridinamine,
- 5-Chloro-N-[3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl]-2-pyridinamine,
- 10 6-Chloro-N-[3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl]-2-pyridinamine,
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-6-methyl-2-pyridinamine,
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-1,3-benzothiazol-2-amine,
- N-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl]-1,3-benzoxazol-2-amine,
- 6-Chloro-N-[3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl]-2-pyrazinamine,
- 15 6-Chloro-N-[3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propyl]-3-pyridazinamine,
- 6-(3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]propyl)amino)-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione,
- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2,6-dimethoxy-4-pyrimidinamine,
- N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-N~2~,N~2~-dimethyl-2,4-
- 20 pyrimidinediamine,
- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-2-[(methylsulfanyl)methyl]-4-pyrimidinamine,
- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-5-methoxy-2-(methylsulfanyl)-4-pyrimidinamine,
- 25 N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-6-methyl-2-(methylsulfanyl)-4-pyrimidinamine,
- N-[2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl]-5-methoxy-2-methyl-4-pyrimidinamine, and
- N~4~-{2-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]ethyl}-6-methyl-N~2~-phenyl-2,4-
- 30 pyrimidinediamine.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises

(i) when T represents a group C(O)NH, reacting a compound of general formula

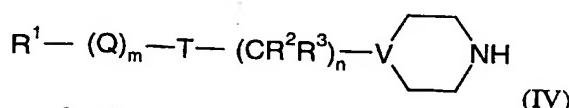


wherein L^1 represents a leaving group (e.g. a hydroxyl or halide, such as chloride, group) and R^1 , m and Q are as defined in formula (I), with a compound of general formula

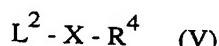


or an acid addition salt thereof (e.g. trifluoroacetate) wherein n , R^2 , R^3 , V , W , X and R^4 are as defined in formula (I); or

15 (ii) when T represents a group C(O)NH and W represents a nitrogen atom, reacting a compound of general formula

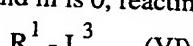


wherein R^1 , m , Q , T , n , R^2 , R^3 and V are as defined in formula (I), with a compound of general formula



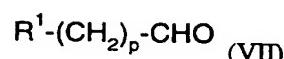
wherein L^2 represents a leaving group (e.g. a halogen atom) and X and R^4 are as defined in formula (I); or

25 (iii) when T represents a group NH and m is 0, reacting a compound of general formula



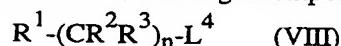
wherein L^3 represents a leaving group (e.g. a halogen atom) and R^1 is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

(iv) when T represents a group NH, m is 1 and Q represents C₁-C₄ alkylene, reacting a compound of general formula

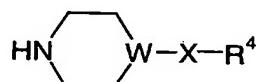


5 wherein p is 0, 1, 2 or 3 and R¹ is as defined in formula (I), with a compound of formula (III) as defined in (i) above; or

(v) when T represents a bond and m is 0, reacting a compound of general formula



10 wherein L⁴ represents a leaving group such as a halogen atom (e.g. chlorine) and n, R¹, R² and R³ are as defined in formula (I), with a compound of general formula



15 (IX)

wherein W, X and R⁴ are as defined in formula (I);

and optionally after (i), (ii), (iii), (iv) or (v) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or

20 solvate of the compound of formula (I).

11. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

30

13. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in therapy.
14. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in therapy.
5
15. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.
10
16. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9.
15

1
INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00563

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, C07D 401/06, C07D 211/14, C07D 211/22, A61K 31/445,
A61P 11/00, A61P 19/00, A61P 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5210086 A (PASCAL, GEORGE ET AL), 11 May 1993 (11.05.93) --	1-16
X	US 5143923 A (NICHOLAS J. HRIB ET AL), 1 Sept 1992 (01.09.92) --	1-16
X	US 4853393 A (ZIMMERMANN, MARKUS), 1 August 1989 (01.08.89) --	1-16
X	US 4335127 A (VANDERBERK JAN ET AL), 15 June 1982 (15.06.82) --	1-16

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document but published on or after the international filing date
"I"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2000	04-08-2000

Name and mailing address of the ISA / Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Eva Johansson/gh Telephone No. + 46 8 782 25 00
--	--

2
INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00563

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9742956 A1 (SYNAPTIC PHARMACEUTICAL CORPORATION), 20 November 1997 (20.11.97) --	1-16
X	EP 0288563 A1 (EISAI CO., LTD), 2 November 1988 (02.11.88) --	1-16
X	EP 0184258 A2 (JANSSEN PHARMACEUTICA N.V.), 11 June 1986 (11.06.86) --	1-16
X	EP 0124476 A1 (CIBA-GEIGY AG), 7 November 1984 (07.11.84) --	1-16
X	FR 2724382 A1 (SYNTHELABO SOCIETE ANONYME), 15 March 1996 (15.03.96) --	1-16
X	STN International, File CAPLUS, CAPLUS accession no. 1997:259827, Document no. 127:17595, Kyorin Pharmaceutical Co., Ltd.: "Preparation of benzamide derivatives as gastrointestinal movement modulators" & JP,A2,09077742,19970325 --	1-16
X	STN International, File CAPLUS, CAPLUS accession no. 1997:204127, Document no. 126:212045, Yamonuchi Pharma Co Ltd: "Preparation of fused benzene ring derivatives as antidepressant drugs"; & JP,A2,09040646,19970210 --	1-16
X	STN International, File CAPLUS, CAPLUS accession no. 1992:151788, Document no. 116:151788, Daiichi Seiyaku Co.,Ltd.: "Preparation of pyrimidine derivatives as serotonin 2 receptor antagonists with high selectivity"; & JP,A2,03264579,19911125 --	1-16

INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 00/00563
--

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.Med.Chem., Volume 37, 1994, Nicholas J. Hrib et al, "Benzisoxazole- and Benzisothiazole-3-carboxamides as Potential Atypical Antipsychotic Agents" page 2308 - page 2314 --	1-16
X	J.Med.Chem., Volume 35, 1992, Jeff L. Herndon et al, "Ketanserin Analogues: Structure-Affinity Relationships for 5-HT2 and 5-HT1c serotonin receptor binding" page 4903 - page 4910 --	1-16
X	Journal of Labelled Compounds and Radiopharmaceuticals, Volume 25, No 7, November 1987, Cor G.M. Janssen et al, "Synthesis of 3H and 14C ketaserin" page 783 - page 792 -----	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00563

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **16**
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. Claims Nos.: **1-16**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00563

Present claims 1-16 relate to an extremely large number of possible compounds. In fact, the claim contains so many options, variables, possible permutations and provisions that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, the search has been carried out for those parts of the application which appear to be clear and concise, namely the examples and closely related homologous compounds etc., those mentioned in the description.

"The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims(s) is impossible. Consequently, the search has been restricted.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99	International application No. PCT/SE 00/00563
Patent document cited in search report	Publication date
US 5210086 A	11/05/93

AU 637261 B 20/05/93
AU 8487191 A 09/04/92
CA 2052609 A 03/04/92
CS 9102999 A 15/04/92
EP 0480794 A 15/04/92
FI 914611 A 03/04/92
FR 2667317 A,B 03/04/92
IL 99612 D 00/00/00
JP 4273870 A 30/09/92
MX 9101341 A 05/06/92
NO 913843 A 03/04/92
NZ 240055 A 25/09/92
PT 99138 A 31/12/93

US 5143923 A	01/09/92
AT 142628 T 15/09/96 AU 644054 B 02/12/93 AU 1518792 A 05/11/92 CA 2067404 A 30/10/92 CS 9201298 A 18/11/92 CZ 282764 B 15/10/97 DE 69213544 D,T 27/02/97 DK 511610 T 16/06/97 EP 0511610 A,B 04/11/92 SE 0511610 T3 ES 2094843 T 01/02/97 FI 921875 A 30/10/92 GR 3021211 T 31/12/96 HU 214032 B 29/12/97 IE 77036 B 19/11/97 IL 101700 A 27/11/95 JP 2656189 B 24/09/97 JP 5132472 A 28/05/93 MX 9201963 A 01/11/92 NO 180488 B,C 20/01/97 NO 921654 D 00/00/00 NZ 242479 A 24/02/95 PL 168090 B 31/01/96 PL 168870 B 30/04/96 RU 2039057 C 09/07/95 US 5225412 A 06/07/93	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/SE 00/00563

02/12/99

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0288563 A1	02/11/88	SE 0288563 T3 AT 105550 T AU 599339 B AU 6405486 A DE 3689836 D, T DK 273788 A FI 90533 B, C FI 882369 A NO 175055 B, C WO 8802365 A	15/05/94 19/07/90 21/04/88 22/09/94 19/05/88 15/11/93 19/05/88 16/05/94 07/04/88
EP 0184258 A2	11/06/86	SE 0184258 T3 AT 75741 T CA 1246074 A DE 3585990 A JP 2009087 C JP 7045492 B JP 61148175 A US 4665075 A	15/05/92 06/12/88 11/06/92 11/01/96 17/05/95 05/07/86 12/05/87
EP 0124476 A1	07/11/84	SE 0124476 T3 AT 35257 T AU 583470 B AU 2542484 A CA 1273929 A CY 1576 A DD 220308 A DE 3472251 A DK 114684 A DK 159420 B, C ES 544713 A ES 553050 A FI 80019 B, C FI 840867 A HK 18491 A IE 57057 B IL 71185 A JP 1844916 C JP 59186959 A NO 840889 A NZ 207428 A PH 21416 A PT 78212 A, B SG 91490 G US 4559349 A ZA 8401728 A GR 82643 A	15/07/88 04/05/89 13/09/84 11/09/90 20/12/91 27/03/85 28/07/88 10/09/84 15/10/90 16/01/87 16/10/87 29/12/89 10/09/84 22/03/91 08/04/92 30/06/88 25/05/94 23/10/84 10/09/84 06/03/87 15/10/87 01/04/84 18/01/91 17/12/85 28/11/84 07/02/85
FR 2724382 A1	15/03/96	NONE	

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
PCT/SE 00/00563

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4335127 A	15/06/82	AT 5258 E,T AU 536175 B AU 5438180 A CA 1132557 A CS 223977 B CY 1252 A DK 7280 A DK 170669 B EP 0013612 A,B SE 0013612 T3 ES 487537 A FI 66609 B,C FI 800047 A GR 67304 A HK 76284 A HR 930474 B IE 49351 B IL 59084 A JP 1497429 C JP 55105679 A JP 63046753 B KR 8500683 B KR 8500684 B LU 88219 A MY 55587 A NO 800034 A NZ 192551 A PH 17114 A PT 70662 A RO 79148 A SG 48684 G SI 8010046 A US 4522945 A YU 4680 A YU 42957 B ZA 8000082 A	15/11/83 19/04/84 17/07/80 28/09/82 25/11/83 31/08/84 09/07/80 27/11/95 23/07/80 16/12/80 31/07/84 09/07/80 29/06/81 19/10/84 31/08/97 18/09/85 29/02/84 29/05/89 13/08/80 19/09/88 14/05/85 14/05/85 03/02/94 31/12/87 09/07/80 06/07/84 01/06/84 01/02/80 17/08/82 29/03/85 31/12/94 11/06/85 30/06/83 28/02/89 26/08/81
WO 9742956 A1	20/11/97	AU 3008297 A	05/12/97

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.	
PCT/SE 00/00563	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4853393 A	01/08/89	AU 4744985 A	20/03/86
		DD 237165 A	02/07/86
		DK 416885 A	15/03/86
		DK 416985 A	15/03/86
		EP 0174653 A	19/03/86
		EP 0174654 A	19/03/86
		ES 546945 A	16/11/86
		ES 546946 A	16/02/87
		ES 554487 A	01/07/87
		ES 554488 A	01/12/87
		FI 853477 A	15/03/86
		FI 853478 A	15/03/86
		GR 852215 A	14/01/86
		GR 852216 A	14/01/86
		IL 76366 A	31/07/89
		JP 61072751 A	14/04/86
		JP 61072752 A	14/04/86
		NO 853609 A	17/03/86
		NZ 213461 A	27/07/89
		PT 81116 A,B	01/10/85
		PT 81117 A,B	01/10/85

THIS PAGE BLANK (USPTO)

92-013607/02 503

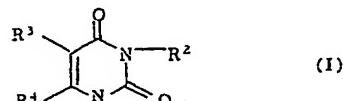
503

DAUC 14.03.90

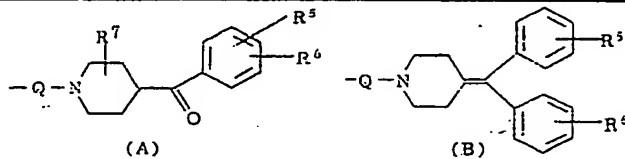
DAUC 14.03.90

DAICHI PHARM CO LTD
14.03.90-JP-063910 (25.ii.91) A61k-31/50 C07D-401/06
New pyrimidine deriv. inhibitors for serotonin and alpha-1
receptors - used for treating circulatory diseases e.g. cerebral
angiopathy, cr psychosis e.g. depression or schizophrenia
C92-006078

Pyrimidine derivs. of formula (I) and their salts are new:



one of R¹ and R² = H, lower alkyl or aralkyl;
the other = gp. (A) or (B);



$Q = 1-8C$ alkylene;

R^5 and R^6 = H, halo, lower alkyl or lower alkoxy;

R^7 = H, OH, lower alkyl or phenyl;

R^3 and R^4 = H, alkyl, phenyl or aralkyl;

or $R^3 + R^4 = 3-5C$ alkylene forming a 5-7 membered ring together with two carbon atoms of the pyrimidine ring.

USE

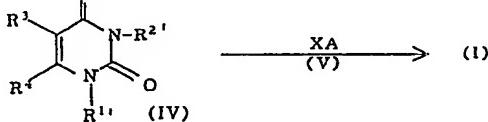
(I) strongly inhibit serotonin receptors and α -1 receptors. The action is long lasting. (I) are useful in treatment of circulatory diseases, e.g. ischaemic heart disease and cerebral angiopathy, or psychoses, e.g.

J03264579-A+

depression and schizophrenia.

PREPARATION

(a) 0



one of R^{11} and $R^{22} = H$, lower alkyl or aralkyl;
the other = H;

X = halo, tosyloxy or mesyloxy.
 Reaction is in an organic solvent, e.g. DMFA, DMSO, MeCN, DMAA, N-methylpyrrolidone or benzene, in the presence of a base, e.g. Na₂CO₃, K₂CO₃ or Et₃N, and if required, an alkali metal iodide, e.g. NaI or KI, at room temp. or at reflux.

EXAMPLE

A soln. of 1.78g. 1-acetyl-5-phenyl-2,4(1H,3H)-pyrimidinedione, 2.15g. 2-[4-(4-fluorobenzoyl)piperidin-

1-yl]ethanol and 2.61g. Ph₃P in 70 ml. DMFA was treated dropwise with 1.73g. diethyl azodicarboxylate under ice cooling and stirring over 15 mins. After stirring for 2 hrs., the solvent was distilled off and the residue dissolved in CHCl₃. Insol. (5-phenyl-2,4(1H,3H)-pyridinedione (0.95g., 60%) was removed by filtration. The filtrate was evapd. in vacuo, and the residue chromatographed on a silica gel column (4-5% MeOH/CHCl₃) to give 0.54g. 3-[2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl]-5-phenyl-2,4(1H,3H)-pyrimidinedione (14%) as colourless crystals. m.pt. 190-191°C. (18ppW52#BDwgNo0/0)

J03264579-A

THIS PAGE BLANK (USPTO)